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Taxonomy, Biology, and Clinical Aspects of *Fusarium* Species†

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INTRODUCTION

Fusarium species have been important for many years as plant pathogens causing diseases such as crown rot, head blight, and scab on cereal grains; vascular wilts on a wide range of horticultural crops; root rots; cankers; and other diseases such as pokkah-boeng on sugarcane and bakanae disease of rice (28). In the last 20 years, *Fusarium* species have been studied extensively because the mycotoxins they produce can be a threat to animal and human health (124). Mycotoxins are secondary metabolites produced by fungi that are associated with a variety of animal diseases and some human health problems (123). More recently, *Fusarium* species have become important as pathogens of human patients with compromised immune systems (6, 8).

Fusarium species are widely distributed in soil and on subterranean and aerial plant parts, plant debris, and other organic substrates (28, 32, 79, 255). They are common in tropical and temperate regions and are also found in desert, alpine, and arctic areas, where harsh climatic conditions prevail (28, 32, 35, 59, 77, 78, 80, 92, 98, 110, 117, 162–164, 242, 251, 255). Many *Fusarium* species are abundant in fertile cultivated and rangeland soils but are relatively uncommon in forest soils (32, 35, 38, 92, 117, 214, 226). *Fusarium* species are often regarded as soilborne fungi because of their abundance in soil and their frequent association with plant roots, as either parasites or saprophytes. However, many have active or passive means of dispersal in the atmosphere and are common colonizers of aerial plant parts, where they may result in diseases of considerable economic importance (27, 33, 59, 60, 89, 113, 118, 150, 165, 204). Some of these airborne *Fusarium* species are encountered rarely in isolations of cultures from soil or roots. The widespread distribution of *Fusarium* species may be attributed to the ability of these fungi to grow on a wide range of substrates and their efficient mechanisms for dispersal (32).

HISTORY OF *FUSARIUM* SYSTEMATICS

The taxonomy of *Fusarium* species has always been a controversial issue. At one time, there were more than 1,000 species, varieties, and forms named on the basis of superficial observations, with little or no regard for the cultural characteristics of these specimens (227). Much of this work was done before pleomorphism and variation in fungi were recognized. Systematists of that era generally did not describe the whole organism and made no attempt to look for similarities or relationships between fungi. The necessity for a precise and reliable system of classification became apparent when it was shown that *Fusarium* species caused serious diseases on many plants. H. W. Wollenweber spent his career studying the genus *Fusarium* (252–254, 256), and these studies resulted in the publication of *Die Fusarien* in collaboration with O. A. Reinking (255). In this publication, the authors reduced the number of *Fusarium* species, varieties, and forms to 142 and grouped these into 16 sections. Since then, and as a result of increased knowledge of variation in fungi, further advances in the taxonomy of *Fusarium* species have occurred. Other taxonomic systems have been proposed by Gerlach and Nirenberg (71), Raillo (182, 183), Bilai (23, 24), Joffe (97), Snyder and Hansen (209–211), Messiaen and Cassini (138), Matuo (133), Gordon (73–80), Booth (28), and Nelson et al. (154), and these will be discussed in detail later in this paper. It is essential to remember that all so-called modern systems of *Fusarium* taxonomy are based on the work of Wollenweber and Reinking (255). *Fusarium* taxonomists may be divided into "splitters," "lumpers," and "moderates." These terms explain the philosophy employed by taxonomists in determining *Fusarium* species but are not necessarily a reflection of the number of species recognized.

Splitters

Wollenweber and Reinking. In 1935, Wollenweber and Reinking published their monumental work on *Fusarium* taxonomy (255) that has become the standard reference on this subject. Wollenweber and Reinking began with approximately 1,000 named species of *Fusarium* and organized these into the 16 sections: *Eupionnotes*, *Macroconia*, *Spicarioides*, *Submicrocera*, *Pseudomicrocera*, *Arachnites*, *Sporotrichiella*, *Roseum*, *Arthrosporiella*, *Gibbosum*, *Discolor*, *Lateritium*, *Liseola*, *Elegans*, *Martiella*, and *Ventricosum*. These sections contained 65 species, 55 varieties, and 22 forms. One can begin to appreciate the magnitude of this task by noting that Wollenweber and Reinking list 77 synonyms for *Fusarium avenaceum* (Fr.) Sacc. alone and 133 synonyms for *F. lateritium* Nees and its teleomorph (255).

A distinct set of characters was used to separate the species, varieties, and forms. The characters used to separate sections were (i) the presence or absence of microconidia, (ii) the shape of the microconidia, (iii) the presence or absence of chlamydospores, (iv) the location of the chlamydospores (intercalary or terminal), (v) the shape of the macroconidia, and (vi) the shape of the basal or foot cells on the macroconidia.

The sections were divided into species, varieties, and forms on the basis of (i) the color of the stroma, (ii) the presence or absence of sclerotia, (iii) the number of septations in the macroconidia, and (iv) the length and width of the macroconidia. For instance, in section *Elegans*, great emphasis was placed on measurements of the length and width of macroconidia; species, varieties, and forms were separated on the basis of a difference in length or width of a few micrometers and on the number of septations in the macroconidia. Each isolate studied was grown on six different media; beerwort agar, carrot decoction agar, oatmeal agar, rice mash, alfalfa stems, and barley heads. In some cases, potato dextrose agar and potato pieces also were used. By studying cultures grown on these media, workers tended to emphasize differences rather than similarities and to exaggerate minor differences, such as length and width of macroconidia, which results in finer and finer separations at the species, variety, and form levels. The system produced is so complex that it is difficult or impossible to use it to construct a satisfactory practical key. The characters used by Wollenweber and Reinking to separate species, varieties, and forms are not stable and can be altered readily by growing cultures on various media and under various environmental conditions.

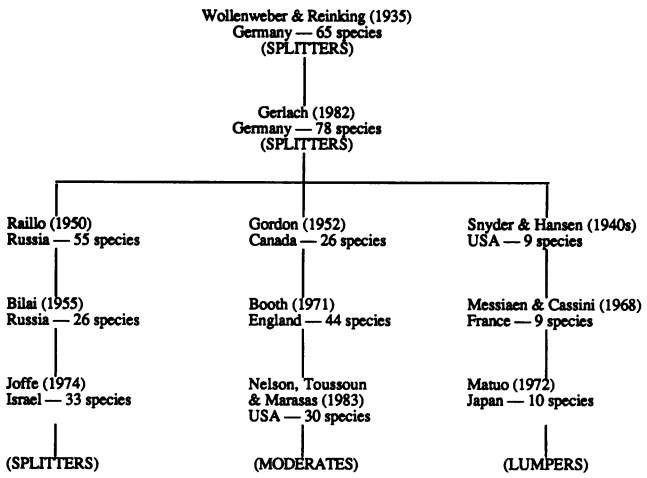

FIG. 1. Relationship of several taxonomic systems to the taxonomic system of Wollenweber and Reinking. Also shown is the relationship of taxonomists classified as splitters, lumpers, and moderates to each other and to Wollenweber and Reinking.

Two other problems also may be responsible in part for the complexity of this system. Cultural variation or mutation in *Fusarium* may not have been recognized by Wollenweber and Reinking, and since their cultures were not started from single conidia, a few of their species and many of their varieties and forms may be cultural mutants of *Fusarium* species. In addition, some species may have been named on the basis of only one or two cultures. One must examine a large number of representative cultures of the organism to determine the range of variation that may occur within that organism. An examination of only one culture of a fungus cannot reveal the range of variation that may occur; it can, however, produce considerable confusion and difficulty for others attempting to identify these species.

Figure 1 shows the relationship of several other taxonomic systems to that of Wollenweber and Reinking (255) and to each other. In Fig. 1, Wollenweber and Gerlach are splitters, with additional splitters on the left and lumpers on the right. Gordon (76), Booth (28), and Nelson, Toussoun, and Marasas (154) are listed in the middle because they have followed a more moderate philosophy or have combined the results of others with their own research to produce a taxonomic system.

Gerlach and Nirenberg. Gerlach (70, 71) continued the work in Wollenweber's laboratory at the Biologische Bundesanstalt, Berlin, until he retired. Both his philosophy and the techniques he used in studying *Fusarium* species and establishing new species placed him with the splitters. This is evident from the 78 species that appear in his atlas recently published with

Nirenberg (71), a well-illustrated work that uses excellent photographs and line drawings to supplement Wollenweber's original drawings included in part. Gerlach and Nirenberg grew cultures on the eight different media used by Wollenweber and Reinking and under conditions that accentuate differences. They concentrated on these differences rather than on similarities, with the result that a slight difference in gross culture morphology may have been the basis for designating a new species or variety. New species were established on the basis of a single culture and, in some cases, on a single mutant culture. This philosophy led to a complex taxonomic system that is difficult to use for the same reasons that Wollenweber and Reinking's system is difficult to use.

Raillo and Bilai. The systems of Raillo (182, 183) and Bilai (23, 24) are not as well understood as other systems (Fig. 1). Raillo studied morphological characters useful in taxonomy and concluded the following: the form of the apical cell was the guiding character in species determination; the incurvature of conidia, length of the apical cell, number of septa, and width of conidia were the characters used in separating subspecies and varieties; and cultural characters such as pigment, presence of sclerotia, and mode of spore formation were useful in separating forms only. She also studied variability in *Fusarium* by initiating cultures from single conidia and found that the form of the apical cell and the incurvature of conidia remained constant in cultures developed from single conidia; the number of septa was constant in isolates within a single-conidium culture; the length and width of conidia varied considerably in separate isolates within a single-conidium culture; the number of sclerotia varied greatly in separate isolates within a single-conidium culture; and the mode of spore formation (pionnotes, pseudopionnotes, and sporodochia) varied in separate isolates within a single-conidium culture.

Bilai (23, 24) recognized the importance of cultural variation or mutation in *Fusarium* taxonomy. She did a critical analysis of several characters used in *Fusarium* taxonomy by studying experimental variability of individual isolates and establishing the range of variation for some species. In addition, she studied experimental morphogenesis in single-conidium isolates in culture, paying particular attention to the effects of temperature, moisture, length of growth period, and composition of the medium, as well as to the method of germination and aging of conidia. Her results showed that the range of variability was greater than that accepted in the description of many species and often included the features of the whole section. On the basis of these results, she revised the taxonomy of the genus to include only nine sections, 26 species, and 29 varieties. Some of her changes, such as combining section *Liseola* with section *Elegans* and combining section *Gibbosum* with section *Discolor*, are difficult to understand. This system may have been used in Russia, but it has not been accepted and used in other parts of the world.

Joffe. Joffe (97) began working on *Fusarium* in the late 1940s in Russia and later immigrated to Israel and continued his work. He examined a large number of isolates of *Fusarium* from soil, wilting or decaying plants, and seed. These isolates were collected in the warm, semiarid climate of Israel and the cold climate of Russia. Other isolates were received from research institutes in several countries. His philosophy and approach to *Fusarium* taxonomy is similar to that of Wollenweber and Reinking (255) and Gerlach (70, 71). In fact, his so-called modern system appears to be simply a restatement of Wollenweber and Reinking's sections and species with the addition of some names by Gerlach. He included 13 sections, 33 species, and 14 varieties.

Lumpers

Snyder and Hansen. Snyder and Hansen (209–211) are considered the ultimate lumpers. In the 1930s, W. C. Snyder went to Berlin and spent a year working with Wollenweber. When Snyder returned to Berkeley, he began an extensive research program on the biology and taxonomy of *Fusarium* species in cooperation with H. N. Hansen, who pioneered the use of single-conidium cultures. In the 1940s, they published their results of studies on the taxonomy of *Fusarium* species in three papers (209–211). In essence, they made nine species out of Wollenweber and Reinking's 16 sections. Snyder and Hansen's system is based primarily on the morphology of the macroconidia and an extensive study of the general nature and variability of *Fusarium* species. The basis for their work was an extensive single-conidium analysis of cultures of *Fusarium* species under identical conditions of substrate and other environmental conditions. These studies revealed a great range of variability in conidial length, width, and septation, in kinds and intensities of pigments produced, and in the presence or absence of sporodochia and sclerotia among the subcultures of the same original single-conidial culture. Working with section *Elegans*, they found that progeny of a single parent may be placed in different species and even in different subsections. This was an indication that the characters used for identification to species level by Wollenweber and Reinking were too narrow.

Snyder and Hansen's work with *F. oxysporum* Schlecht. emend. Snyd. & Hans. (section *Elegans*) is the basis for their system (209). This work illustrated the importance of cultural variation in taxonomy and is generally accepted. Their work with *F. solani* (Mart.) Sacc. emend Snyd. & Hans., which is also generally accepted, showed that the variations are inheritable (209). The remaining work, including the lumping of several sections into one species, is not generally accepted (211). The lumping of Wollenweber and Reinking's sections *Arthrosporiella*, *Discolor*, *Gibbosum*, and *Roseum* into *F. roseum* Link has caused a great deal of confusion and controversy. The reduction in recognized species eliminated the convenience of naming certain fungi that previously had been known by species names. The members of these sections that were pathogenic on cereals were further distinguished by the forma specialis name *cerealis*. Later, Snyder and his colleagues proposed the adoption of the nonbotanical name, cultivar, for certain infraspecies populations differing in conidial morphology (213). They state, "The cultivar provides a means of informally naming plants. It has nothing to do with taxonomy or classification, and therefore is entirely independent of the botanical variety which implies relationship and position in a scheme of plant classification. These two systems of naming serve different purposes and may supplement one another, but neither takes the place of the other." Following these proposals, if one had a pathogenic strain of *F. graminearum* Schwabe, it would be written *F. roseum* f. sp. *cerealis* 'Graminearum.' If the strain was not pathogenic, the name would be *F. roseum.*

There is a fundamental flaw in the cultivar concept because Snyder et al. (213) considered it an informal device. Consequently, they proposed only a few cultivars that they did not describe and thus left no formal guidelines for future workers. Later, Nash and Snyder (146) and Snyder and Nash (214) named additional cultivars without descriptions. In short, the concept of cultivars was never completely explained or finalized.

On the basis of continued study and usage, it has been concluded that the concept of a single species, *F. roseum* as proposed by Snyder and Hansen (211), cannot be justified and

should be abandoned. The reasons for this conclusion are as follows. (i) The reduction of all species in sections *Roseum*, *Arthrosporiella*, *Gibbosum*, and *Discolor* was an oversimplification based on insufficient cultural studies and largely an extrapolation from earlier work on sections *Elegans*, *Martiella*, and *Ventricosum* (209, 210). (ii) There are no substantial morphological characters common to all populations included in *F. roseum* by Snyder and Hansen. A few characters are common to most populations, but taxonomically these are of secondary importance. Most populations are reported to form chlamydospores, but their formation is erratic in culture. Within populations, the formation of microconidia and chlamydospores can be highly variable even under standard conditions. Thus, there is no sound biological reason for placing these populations within a single species on the basis of morphological characteristics (154). (iii) The species in *Fusarium* sections *Roseum*, *Arthrosporiella*, *Gibbosum*, and *Discolor* are distinct and can be recognized and separated (154, 255). (iv) The designation f. sp. *cerealis* to denote pathogenicity to cereals is not valid as shown by Tammen (223), and his suggestion to use f. sp. *cerealis* simply to designate pathogenesis is confusing and unnecessary. (v) The use of trinomials and quadrinomials as names is unnecessary, cumbersome, and confusing. (vi) The use of the name *F. roseum* f. sp. *cerealis* and cultivar names has caused confusion and misunderstanding in regard to the correct identification of fungi in these sections and, for mycologists, plant pathologists, mycotoxicologists, and others working with these species, has reduced the value of publications in which the name *F. roseum* is used (125).

Messiaen and Cassini. Messiaen and Cassini (138) followed Snyder and Hansen's system, but they used botanical varieties instead of cultivars at the subspecies level in *F. roseum*. They provided descriptions for each variety, and a key was provided for the entire system.

Matuo. Matuo (133) also followed the Snyder and Hansen system and provided a key to the entire system. Matuo and Kobayashi (134) reported that *Hypocrea splendens* Phil. & Plowr. produced a conidial state that they named *F. spendens*. However, further work showed that this was most likely a *Nectria* hyperparasite (29). Matuo was also in favor of lumping *F. lateritium* and *F. roseum*, but this concept has received very little support.

Moderates

Gordon. Gordon worked in Canada from the 1930s to the 1960s with *Fusarium* species isolated from cereal seed, various host plants, and soil from both temperate and tropical geographic areas (73–80). His taxonomic system was a compromise between that of Wollenweber and Reinking (255) and Snyder and Hansen (209–211) but is more closely allied to that of Wollenweber and Reinking.

Booth. Booth (28) modified Gordon's system, added information from his studies, and expanded the information on perfect states (29). A major contribution was information on conidiophores and conidiogenous cells useful in the taxonomy of *Fusarium* species. He showed the value of the presence of polyphialides versus monophialides in separating sections and species. The length and shape of the microconidiophores also were shown to be reliable characters in separating *F. oxysporum*, *F. solani*, and *F. moniliforme* Sheldon. Booth made a real effort to bridge the gap between the taxonomic mycologists and plant pathologists and other groups that work with these organisms.

Nelson, Toussoun, and Marasas. The philosophy of Nelson, Toussoun, and Marasas is set forth in two publications (148, 154). In these publications, they point out that there is no single taxonomic system in use today that is completely satisfactory for the identification of all *Fusarium* species. The continued proliferation of "new" or "modern" systems for the taxonomy of *Fusarium* species does not solve the problem. New or modern systems for the taxonomy of *Fusarium* species that ignore the collective wisdom and errors of past research are likely to be counterproductive to the development of a better practical taxonomic treatment of the genus (148). On this basis, these workers (154) selected what they considered the best parts of several systems and combined them with results of their own research to develop a compromise system in which utility for practical identification was emphasized. The system included *F. oxysporum* and *F. solani*, as described by Snyder and Hansen (209, 210), and information on conidiophores, especially that on microconidiophores, as described by Booth (28). The sections of Wollenweber and Reinking (255) containing toxigenic species as well as some other sections were retained. However, the number of species was reduced, and varieties and forms were combined with the appropriate species. In their opinion, these changes were justified because many of the varieties and forms may have been cultural variants or mutants. The publication of Nelson et al. (154) is illustrated with photographs of macroconidia, microconidia, conidiophores, and chlamydospores produced on carnation leaf agar (54). *Fusarium* species grow well on this medium, produce sporodochia readily, and produce uniform conidia of typical morphology suitable for observation and identification of *Fusarium* species. Their book is cross-referenced to the taxonomic systems of Wollenweber and Reinking (255), Gerlach and Nirenberg (71), Booth (28), Joffe (97), Snyder and Hansen (209–211), and Messiaen and Cassini (138), and the index lists all known species names from these systems. If the species name is not known, synoptic keys are provided for identification of sections and species.

TAXONOMY

Many species, populations within species, and unidentified populations in the genus *Fusarium* exhibit a remarkable degree of variation with respect to morphological, cultural, and physiological characteristics. This capacity for variation may explain, in part, the ability of *Fusarium* species to colonize diverse ecological niches in most geographic areas of the world. However, variation has led to considerable difficulties in the development of a stable and widely accepted taxonomic system for the genus. The proliferation in the number of species described prior to 1900 can be attributed in part to variability in many *Fusarium* populations as well as to inadequate criteria for delimiting taxa (227, 255).

During the last decade, mycologists and plant pathologists have reached a reasonable degree of consensus on the taxonomy of *Fusarium* species. The basic approach proposed and illustrated by Nelson et al. (154) and Burgess et al. (33) has been accepted by many workers and is based largely on *Die Fusarien* (255). Since 1982, several new species have been recognized (34, 37, 126, 128, 153) and some species have been emended (36) or transferred to another genus [e.g., *F. stoveri* Booth to *Michrodochium stoveri* (Booth) Samuels and Hallett (200)]. It is not surprising that additional populations of *Fusarium* species distinctive enough to be recognized as new taxa have been identified, as it is only in the last 20 years that intensive and extensive surveys of *Fusarium* populations associated with various crops and soils in the hot semiarid and subtropical regions of the world have been completed (34, 35, 120). Prior to the completion of these surveys, *Fusarium*

taxonomy had been based mainly on material collected in cool temperate regions, although Reinking and Wollenweber (185), Wollenweber and Reinking (254), Gordon (78, 80), and Booth (28) did have access to cultures collected from some tropical regions. It is likely that other populations will be differentiated as further systematic surveys of *Fusarium* species are completed in arid and tropical regions, where information on the nature and distribution of *Fusarium* populations is limited.

The genus *Fusarium* is divided into sections. A section is used for genera with a large number of species to group species with similar morphological characteristics. In some sections in *Fusarium* such as *Elegans* and *Spicarioides*, there is only one species per section. In other sections, such as *Gibbosum* and *Discolor*, there may be five to ten species per section.

General Characteristics of *Fusarium* Species

Fusarium species may produce three types of spores called macroconidia, microconidia, and chlamydospores (154) (Fig. 2 to 13). Some species produce all three types of spores, while other species do not. The macroconidia are produced in a specialized structure called a sporodochium in which the spore mass is supported by a superficial cushionlike mass of short monophialides bearing the macroconidia (85). The sporodochium sometimes may be encased in slime. Macroconidia may also be produced on monophialides and polyphialides in the aerial mycelium (Fig. 14 to 20). A monophialide is a conidiophore with only one opening or pore through which endoconidia are extruded, while a polyphialide has two or more such openings or pores. Some conidia are intermediate in size and shape, and these have been referred to as both macroconidia (154) and mesoconidia (168). These intermediate conidia are found primarily in *F. semitectum* Berk. & Rav., *F. avenaceum*, and *F. subglutinans* (Wollenw. & Reinking) Nelson, Toussoun & Marasas. Until more cultures of each species are studied thoroughly, the use of the term mesoconidia is questionable.

Microconidia are produced in the aerial mycelium but not in sporodochia. They may be produced in false heads only or in false heads and chains (Fig. 21) on either monophialides or polyphialides. False heads occur when a drop of moisture forms on the tip of the conidiophore and contains the endoconidia as they are produced. Microconidia are of various shapes and sizes (Fig. 22), and those produced in chains have a truncate base (Fig. 22). The third type of spore formed by *Fusarium* species is a chlamydospore, which is a thick-walled spore filled with lipidlike material that serves to carry the fungus over winter in soil when a suitable host is not available. The chlamydospores may be borne singly, in pairs, in clumps, or in chains, and the outer wall may be smooth or rough (Fig. 10 to 12).

Primary Characters Used To Separate Species in *Fusarium* Taxonomy

Morphology of the macroconidia. The morphology of the macroconidia is the key characteristic for characterization not only of the species but also of the genus *Fusarium*. Macroconidia of *Fusarium* species are of various shapes and sizes (Fig. 2 to 7), but the shape of the macroconidia formed in sporodochia for a given species is a relatively consistent and stable feature when the fungus is grown on natural substrates under standard conditions (33, 154, 252). Dimensions of the macroconidia may show considerable variation within individual species and should be used cautiously as taxonomic criteria.

Microconidia. The presence or absence of microconidia is a primary character in *Fusarium* taxonomy. If microconidia are present, the features considered are the shape (Fig. 22) and the mode of formation, whether it be singly, in false heads only, or in false heads and chains (Fig. 21). The mode of formation of microconidia is best observed in situ on a natural substrate agar medium such as carnation leaf agar (54).

Microconidiophores. The morphology of the conidiophores bearing the microconidia is a primary taxonomic character. These conidiophores may be either monophialides only (Fig. 14 to 17) or both monophialides and polyphialides (Fig. 18 to 20) in a given species producing microconidia.

Chlamydospores. The presence or absence of chlamydospores is a primary character in *Fusarium* taxonomy. If chlamydospores are present, they may be formed singly, in pairs, in clumps, or in chains, with either rough or smooth walls.

Secondary Characters Useful in Separating Species in *Fusarium* Taxonomy

The following secondary characteristics are useful in describing a species when the cultures are grown under standard environmental conditions of light, temperature, and substrate (33, 154) but should not be regarded as suitable criteria for differentiation of a species: the morphology and pigmentation of the colony, including the presence or absence of sporodochia, sclerotia, or stroma. The pigmentation of colonies grown on carbohydrate-rich media is variable in some species. The pigmentation of the colony may be helpful to someone with experience in *Fusarium* taxonomy but quickly can lead those without prior experience in this area astray. The linear growth rate of the fungus under controlled conditions was used as a taxonomic characteristic by Booth (28) and others (33) but must also be used with caution. Isolates within a species may vary considerably with respect to the secondary characters. The degree of variation shown by a particular secondary character may differ between species. Although the shape of the macroconidia formed in sporodochia on carnation leaf agar is a reliable character, the length and width of the macroconidia are less stable features and should be regarded as secondary characters. The macroconidia of a wide range of isolates of *F. culmorum* (W. G. Smith) Sacc. are relatively uniform in length, whereas the length of macroconidia of *F. equiseti* (Corda) Sacc. varies widely between isolates, even among those from the same geographic location.

PROBLEMS IN WORKING WITH *FUSARIUM* SPECIES

The methods and media used in growing *Fusarium* species for identification are covered in detail in other publications. The reader is urged to consult Nelson et al. (154), Fisher et al. (54, 55), and Klotz et al. (108) for these details.

Transfer Methods

The single-spore method and the hyphal-tip method are the primary means used to initiate and transfer cultures of *Fusarium* species. Since each conidium is of a single genotype, the colony that develops is of that genotype. Mutant cultures that occur can be recognized readily. In this manner, clones can be maintained indefinitely in culture. The hyphal-tip method is used to transfer cultures of *Fusarium* species that mutate rapidly after being transferred by single conidia. This technique involves the transfer of a single hyphal tip rather than a mass transfer from the growing edge of a colony to initiate the culture. The transfer is done under the dissecting microscope, in much the same manner as the transfer of a single germinating conidium.

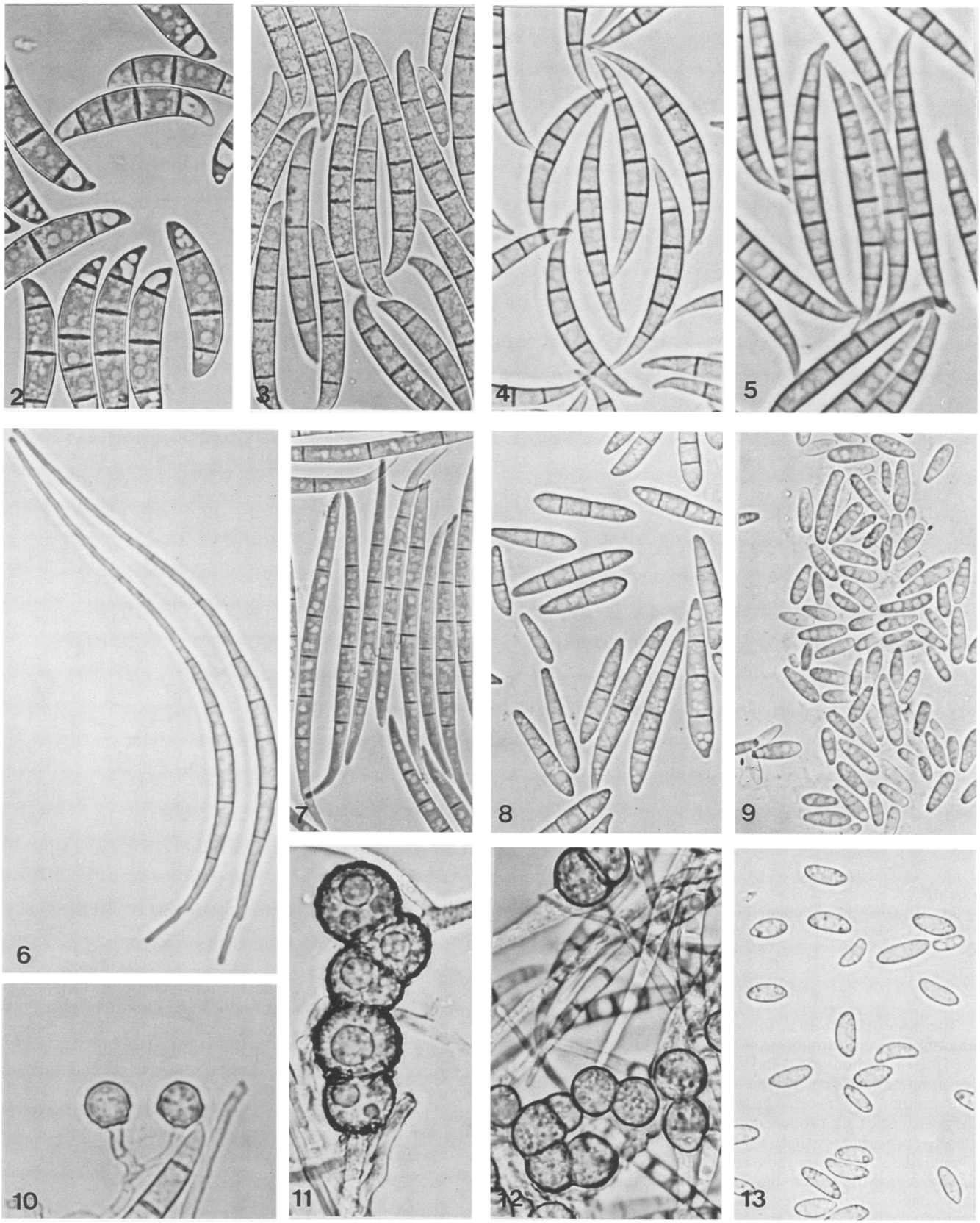

FIG. 2–7. Macroconidia of several *Fusarium* species: 2, *F. culmorum*; 3, *F. solani*; 4, *F. equiseti*; 5, *F. graminearum*; 6, *F. longipes*; 7, *F. avenaceum*. Magnification (each), ×950.

FIG. 8, 9, 13. Microconidia of several *Fusarium* species: 8, *F. scirpi* (magnification, ×1,000); 9, *F. moniliforme* (magnification, ×1,000); 13, *F. solani* (magnification, ×950).

FIG. 10–12. Chlamydospores of several *Fusarium* species: 10, *F. oxysporum*; 11, *F. equiseti* (magnification, ×1,000); 12, *F. solani* (magnification, ×950).

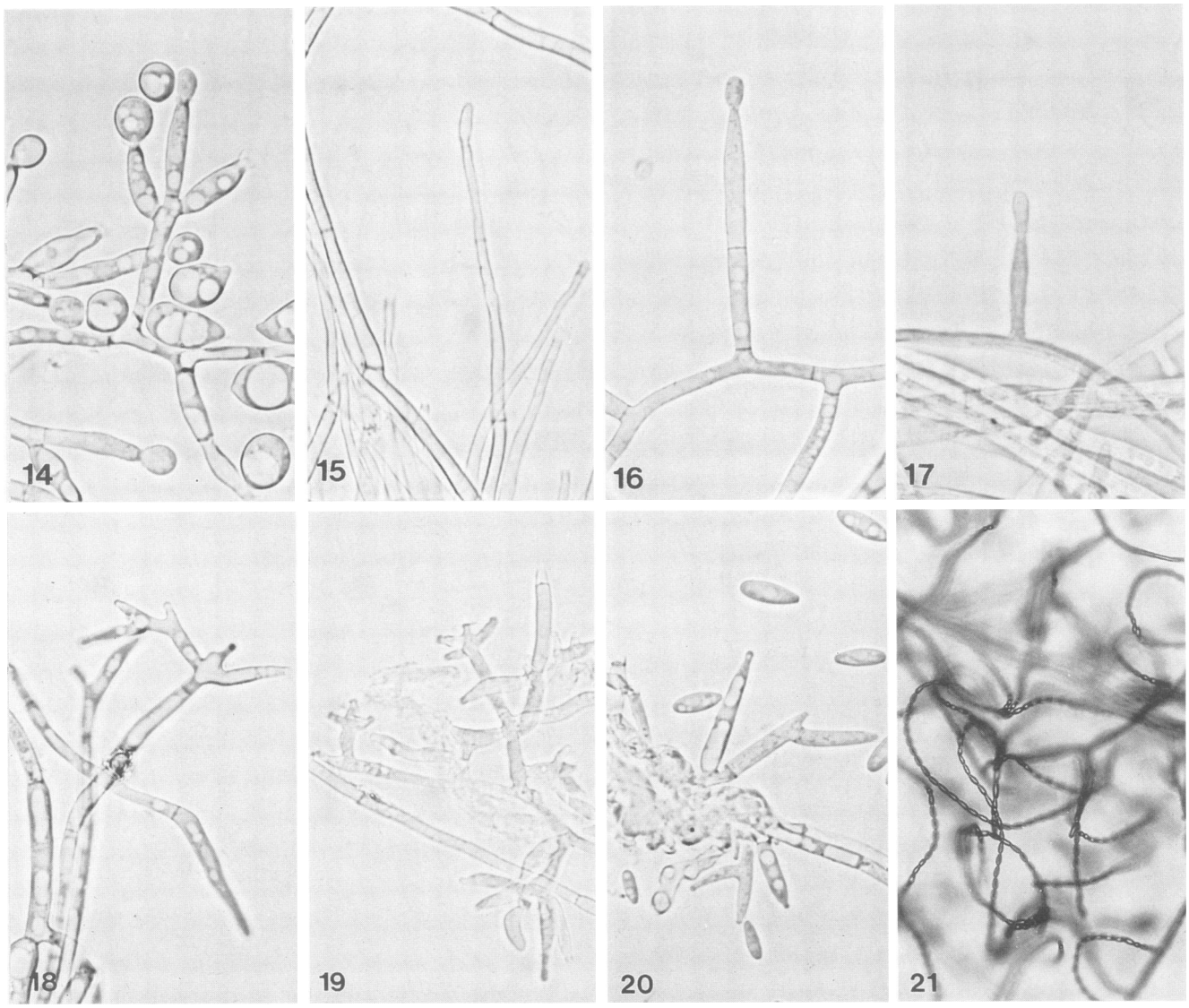

FIG. 14–17. Monophialides of several *Fusarium* species: 14, *F. poae*; 15, *F. solani*; 16, *F. moniliforme*; 17, *F. oxysporum*. Magnification (each), (×970).
FIG. 18–20. Polyphialides of several *Fusarium* species: 18, *F. subglutinans*; 19, *F. scirpi*; 20, *F. proliferatum*. Magnification (each), (×970).
FIG. 21. Microconidia of *F. moniliforme* formed in long chains. Magnification, ×109.

Culture Media

The four media used for growing *Fusarium* species for identification are carnation leaf agar (54), potato dextrose agar (154), KCl medium (55), and soil agar (108).

Carnation leaf agar has the advantage of promoting sporulation rather than mycelial growth. Conidia and conidiophores of most species are produced in abundance, their morphology closely approximates that seen under natural conditions, and phenotypic variation is reduced. The value of carnation leaf agar as a growth medium may be due to the facts that it is low in available carbohydrates and it contains complex, naturally occurring substances of the type encountered by *Fusarium* species in nature. Therefore, the fungi grow and sporulate in a manner similar to that found on a host plant or natural substrate. Identification procedures can be based almost exclusively on cultures grown on this medium.

Potato dextrose agar made according to the specifications of Nelson et al. (154) is a valuable medium used principally for noting gross morphological appearances and colony colorations. Because of its high available carbohydrate content, potato dextrose agar generally emphasizes growth to the detriment of sporulation. Cultures grown on this medium sporulate poorly, frequently taking more than a month to do so. The conidia produced are often misshapen and atypical. Consequently, with few exceptions, potato dextrose agar cultures are not used for microscopic observations. Cultures grown on potato dextrose agar are used only in a secondary role.

KCl medium (55) is used to observe the formation of microconidia in chains by species in section *Liseola*. The species that do form chains of microconidia form more abundant, longer chains on this medium. The chains are easier to observe because there is less moisture on the surface of the agar and fewer droplets of moisture in the aerial mycelium.

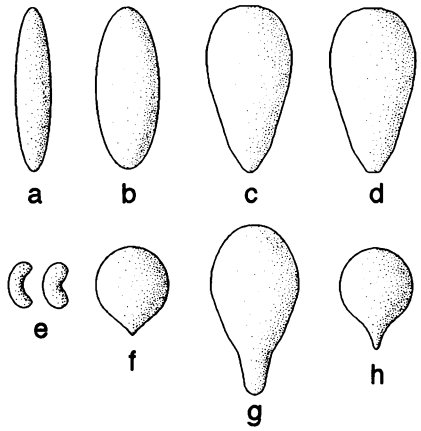

FIG. 22. Shapes of microconidia of various *Fusarium* species: a, fusiform; b, oval; c, obovoid; d, obovoid with a truncate base indicating that the microconidia were formed in a chain; e, allantoid; f, napiform; g, pyriform; h, turbinate.

Direct observation under a microscope of 4- to 5-day-old cultures in petri dishes will demonstrate whether or not chains of microconidia are formed and may reveal the presence of monophialides or polyphialides.

Soil agar (108) is helpful in promoting rapid chlamydospore formation in a number of *Fusarium* species. A large piece of inoculum from an actively growing culture is used to inoculate the soil agar in a petri dish. Chlamydospore formation occurs primarily in the original piece of inoculum, with very few forming in the soil agar itself. Cultures that require up to 30 days for chlamydospore formation on other media may form chlamydospores in 4 to 6 days on soil agar.

Cultural Mutation

The majority of *Fusarium* species isolated from nature produce their macroconidia on sporodochia. The sporodochial type often mutates in culture, especially on media rich in carbohydrates. Mutations may also occur in nature, but are rare. These mutants may give rise to others so that a mutational sequence occurs. In pathogenic isolates, these mutants frequently exhibit a loss of virulence and the ability to produce toxins may be reduced or lost. Variability and its effect on virulence and taxonomy have been discussed in detail elsewhere (90, 166, 178, 207, 208, 212, 239). The mutation sequence has never been shown to reverse itself. The two major types of mutants produced from the sporodochial type are the pionnotal type and the mycelial type. The characteristics of the pionnotal type are (i) the production of little or no aerial mycelium, (ii) the production of abundant macroconidia on the surface of the colony causing the surface to appear shiny and wet, (iii) more intense pigmentation of colonies than of the sporodochial colonies, (iv) the production of longer and thinner macroconidia than those produced by the sporodochial type, and (v) mutants that may be less virulent than the sporodochial type and may also lose the ability to produce toxins. The characteristics of the mycelial type are (i) the production of abundant aerial mycelium, (ii) the production of very few to no macroconidia, (iii) the frequent lack of sporodochia, sclerotia, and pigmentation in culture, and (iv) mutants that may be less virulent than the sporodochial type and may also lose the ability to produce toxins (154).

Procedures that reduce mutant populations include (i) initiating cultures from single conidia, (ii) initiating cultures from single hyphal tips, (iii) avoiding media rich in carbohydrates, and (iv) keeping subculturing to a minimum (154).

TOXIGENICITY OF *FUSARIUM* SPECIES

Mycotoxins and Mycotoxicoses

Mycotoxins are secondary metabolites of fungi that are harmful to both animals and humans. Mycotoxicoses are diseases caused by the ingestion of foods or feeds made toxic by these fungal metabolites. Mycotoxins have been known to be a hazard to human and animal health for many years, and this threat can only become more important as the demand on the available food supply increases. When the food supply is limited, the mycotoxin hazard is increased in at least two ways: (i) more fungus-damaged, potentially mycotoxin-containing foodstuffs are consumed rather than discarded; and (ii) malnutrition enhances the susceptibility to lower levels of foodborne mycotoxins.

Mycotoxicoses are diseases in which multiple factors interact in the causal complex. Some of the factors involved in the occurrence of a field outbreak of a mycotoxicosis caused by a plant-pathogenic fungus are (i) the infection of a susceptible host plant by a pathogenic strain of the mycotoxin-producing fungus, (ii) environmental and other factors favorable to the development of the disease, (iii) genetic capability of the pathogen to produce a metabolite or metabolites harmful to animals or humans, (iv) environmental and other conditions conducive to the elaboration of the mycotoxin(s) and the accumulation of sufficient quantities of these toxic metabolites in the diseased plant to cause a toxicosis in the consumer, and (v) the consumption of sufficient quantities of toxin-containing plant material by a genetically and a physiologically susceptible consumer (123). *Fusarium* species are associated with a number of human and animal mycotoxicoses. A detailed review covering published information through 1981 relating to many of these mycotoxicoses and the toxins involved is given by Marasas et al. (124). A brief review of each of the more important mycotoxicoses is presented here.

Human Diseases Associated with Toxigenic *Fusarium* Species

Alimentary toxic aleukia. Overwintered cereal grains colonized by *F. sporotrichioides* Sherb. caused the deaths of hundreds of thousands of people in the USSR during the closing years of World War II (124). Joffe (98) has reviewed the literature on alimentary toxic aleukia in detail, and the information given below is taken from his review. Other outbreaks of this mycotoxicosis have been recorded in the USSR from time to time probably since the 19th century. In 1932 and 1934, the area of outbreaks expanded, and alimentary toxic aleukia was endemic in several districts of Western Siberia and in other adjacent areas. This mycotoxicosis became widespread in 1942 and appeared again at the beginning of World War II in several republics and districts. During 1944, there were outbreaks of alimentary toxic aleukia in 34 districts and counties of the USSR. In the same year, the scarcity of food forced a large proportion of the population to collect grain that had been left in the fields throughout the winter. In 1945, this mycotoxicosis occurred in 14 other districts and regions. In 1946, it was reported in 19 districts and counties and was reported for the first time in several areas. In 1947, alimentary toxic aleukia appeared in 23 regions. In 1952, 1953, and 1955, severe cases of alimentary toxic aleukia appeared again in a number of regions of the USSR.

This mycotoxicosis occurred in families that had gathered grain from fields after the snow had melted in the spring. The disease usually appeared after at least 2 kg of food prepared from toxic overwintered grain had been consumed. Lesions in the hematopoietic system were the result of a toxic substance accumulating in the body and usually appeared 2 to 3 weeks after the consumption of toxic grain. Prosomillet (*Panicum miliaceum* L.) and wheat (*Triticum aestivum* L.) were found to be the most toxic grains. People consuming a balanced diet were less susceptible to the toxin than people who were suffering from malnutrition. Grain harvested during spring thaws was toxic, while grain harvested during autumn or winter before the snow melted was either nontoxic or slightly toxic (93).

Overwintered cereal grains colonized by *F. sporotrichioides* and *F. poae* (Peck) Wollenw. are the cause of alimentary toxic aleukia (98, 124). The toxin produced by these organisms is called T-2 toxin and was first isolated and characterized by Bamburg (14) and Bamberg et al. (15).

Clinically, alimentary toxic aleukia is usually divided into three stages. If the disease is diagnosed during the first stage, or during the transition from the second to the third stage, early hospitalization and treatment save lives. However, if the disease is not detected until the third stage, the patient's condition is usually critical, and death results.

(i) First stage. The symptoms of the first stage appear a short time after ingestion of toxic grain and include primary changes in the mouth cavity and gastrointestinal tract. The patient feels a burning sensation in the mouth, tongue, throat, palate, esophagus, and stomach since the toxin affects the mucous membranes. Inflammation of the gastric and intestinal mucosa results in vomiting, diarrhea, and abdominal pain. In most cases, excessive salivation, headache, dizziness, weakness, fatigue, and tachycardia occur, and in some cases fever and sweating occur. The first stage may last for 3 to 9 days.

(ii) Second stage. The second stage is often called the latent stage because the patient feels well and is capable of normal activity. The main features are disturbances in the hematopoietic system characterized by a progressive leukopenia, with a granulocytopenia and a relative lymphocytosis. In addition, there are anemia and a decrease in the platelet count, as well as a lowering of the patient's resistance to bacterial infections. This stage usually lasts for 3 to 4 weeks but may be as long as 8 weeks.

(iii) Third stage. The first visible sign of the third stage is the appearance of petechial hemorrhages on the skin of the trunk, in the axillary and inguinal areas, on the lateral surfaces of arms and thighs, on the chest, and, in serious cases, on the face and head. Necrotic changes soon appear in the throat, causing difficulty and pain on swallowing. Secondary bacterial infections often occur in these necrotic sites, and suppression of the patient's immune system and the infection may result in death of the patient.

Urov or Kashin-Beck disease. Urov or Kashin-Beck disease is a chronic disabling, deforming, dystrophic osteoarthosis involving the peripheral joints and spine that occurs endemically among the Cossacks in the valley of the Urov River in eastern Siberia as well as in North Korea and northern China (124). The disease begins slowly and often asymptomatically in children of preschool or school age. In the early stages, patients experience pain in some of their joints and the joints become thickened. The disease then develops slowly and chronically and is manifested as a shortening of the long bones, thickening and subsequent deformity of the joints, flexor contractures, and muscular atrophy.

Climatic peculiarities that occurred in areas where this disease was epidemic were marked temperature changes during the day and the occurrence of the major portion of the rainfall during late summer or early fall when cereals were maturing and grain harvest was in progress. These climatic factors were conducive to a high level of infection by *Fusarium* species in harvested grains. Considerable experimental evidence has been produced in the former USSR that Urov disease is caused by certain strains of *F. poae*, but the mycotoxin(s) involved has not been positively identified and the etiology of the disease has not been resolved (124).

Akakabi-byo (scabby grain intoxication). In Japan, sporadic epidemics of akakabi-byo (red mold disease or scab) of wheat, barley, oats, rye, and rice caused by *F. graminearum* can affect more than one-third of the national production of these cereals. Infected cereal grain is frequently associated with outbreaks of human mycotoxicosis characterized by anorexia, nausea, vomiting, headache, abdominal pain, diarrhea, chills, giddiness, and convulsions. Isolates of *F. graminearum* from scabby cereal grains from Japan are known to produce the trichothecenes deoxynivalenol, nivalenol, fusarenon-X, diacetoxyscirpenol, neosolaniol, and T-2 toxin in culture. An isolate of *F. sporotrichioides* from scabby wheat from Japan produced nivalenol, fusarenon-X, diacetylnivalenol, and T-2 toxin in culture. Scabby cereals in Japan are known to be contaminated with deoxynivalenol and nivalenol and may be infected by both *F. graminearum* and *F. sporotrichioides*. It is possible that synergistic interactions between deoxynivalenol and other tricothecenes may be involved in the human mycotoxicosis caused by the consumption of scabby cereal grains in Japan.

Evidence exists that the consumption of cereals infected by *F. graminearum* has resulted in cases of a human mycotoxicosis characterized by emesis in Japan, Korea, and the former USSR. Although deoxynivalenol and nivalenol are known to occur naturally in scabby cereal grains in Japan, these two trichothecenes have not been directly implicated in cases of human mycotoxicosis. Thus, it is not known if deoxynivalenol and/or nivalenol is responsible for the clinical signs of scabby grain intoxication in humans or if other factors also are involved (124).

Animal Diseases Associated with Toxigenic *Fusarium* Species

Hemorrhagic syndrome. Outbreaks of a hemorrhagic syndrome characterized by bloody diarrhea, necrotic oral lesions, hemorrhagic gastroenteritis, and extensive hemorrhages in many organs occur sporadically in animals such as cattle, pigs, and poultry in the north central United States and elsewhere. The disease is associated with the ingestion of moldy cereals, particularly corn, and some of the most toxic *Fusarium* species have been isolated from these feeds.

F. sporotrichioides and *F. poae* are the fungi most often associated with such feeds. These weakly pathogenic fungi infect the host in the field, develop saprophytically after the death of the host, and produce mycotoxins during overwintering in the field and/or during storage of the harvested host, all of which render the diseased plant toxic when consumed.

The hemorrhagic syndrome in farm animals and alimentary toxic aleukia in humans are closely related, if not identical, syndromes. Both are caused by trichothecene mycotoxins, such as T-2 toxin and diacetoxyscirpenol, produced primarily by *F. sporotrichioides* (123, 124).

Estrogenic syndrome. In many countries, sporadic field outbreaks of hyperestrogenism in animals, particularly pigs, are caused by the consumption of cereals, particularly corn and barley, infected by *F. graminearum* and contaminated with the estrogenic metabolite, zearalenone. Pigs are the most sensitive

animals, and primarily the genitals and reproductive organs are involved. In prepuberal gilts, the vulva becomes swollen, hyperemic, and edematous, the mammary glands are swollen, and in severe cases, there may be vaginal and rectal prolapse. True estrus is not commonly observed, but breeding sows may show prolonged estrus cycles. Young males may undergo a feminizing effect, with enlargement of the mammary glands, atrophy of the testes, and swelling of the prepuce. In mature boars, a marked decrease in libido may occur. Infertility, reduced litter size, and weak piglets are also manifestations of the estrogenic syndrome.

Feed refusal and emetic syndromes. Sporadic field outbreaks of feed refusal by pigs, sometimes associated with vomiting, are caused by the infection of cereals, particularly corn and barley, by *F. graminearum* in the midwestern United States, Japan, and elsewhere. The reduced palatability of the scabby grain is reflected in decreased weight gains and slower growth rates of pigs and is associated with nausea and emesis in animals forced by starvation to eat the grain.

It has been established that the mycotoxin deoxynivalenol occurs in cereals infected by *F. graminearum* and is associated with field outbreaks of feed refusal and emesis in animals, particularly pigs. Deoxynivalenol is found at levels capable of inducing the characteristic clinical signs of these syndromes under experimental conditions. However, there is reason to believe that deoxynivalenol alone is not responsible for all of the feed refusal and emetic activity of *F. graminearum*-infected cereals and that other factors may also be involved (123, 124).

Fescue foot. Winter pastures of tall fescue (*Festuca arundinacea* Schreb.) in the United States, Australia, and New Zealand are associated with sporadic outbreaks of a disease in cattle known as fescue foot. This disease is characterized by lameness, loss of weight, arched back, elevated body temperature, and dry gangrene involving the hind feet, tail tip, and ears, with sloughing of the most distal parts of these extremities. Although the clinical signs of fescue foot are very reminiscent of the gangrenous form of ergot poisoning, ergot sclerotia apparently are not involved in the disease. The typical clinical signs of fescue foot have been reproduced experimentally in cattle with ethanol extracts of toxic fescue hay.

Several *Fusarium* species have been isolated from toxic hay. One strain isolated was identified as *F. sporotrichioides*, and it produces several mycotoxins in culture. However, since these mycotoxins have not been shown to occur naturally in toxic fescue hay, the role of *F. sporotrichioides* in fescue foot of cattle is unknown at present (123).

Degnala disease. Degnala disease occurs during winter in buffaloes and cattle fed almost exclusively on rice straw in low-lying, waterlogged, rice-growing areas of Pakistan and India. The disease is characterized by edematous swelling of the legs and necrosis, gangrene, and sloughing of the extremities. The characteristic clinical signs were reproduced in buffalo calves after feeding them rice straw from farms where field outbreaks had occurred. Later, the disease was reproduced experimentally in buffalo calves fed cultures of an isolate of *F. equiseti* on rice straw. The organism had been isolated from toxic rice straw, but the mycotoxins produced by this strain have not been identified. In addition to *F. equiseti*, some cultures of *F. semitectum* also have been isolated from toxic rice straw. At present, it is not certain whether this disease is caused by *F. equiseti* or *F. semitectum* or both. Since the toxins produced by these strains have not been identified, the etiology of this disease is not known at present (123).

Moldy sweet potato toxicosis (atypical interstitial pneumonia). Field outbreaks of a fatal respiratory disease of cattle in Japan and the United States have been attributed to the ingestion of moldy sweet potatoes (*Ipomoea batateas* L.) for several years. This toxicosis is caused by four lung-toxic furanoterpenoides present in sweet potato tubers infected by *F. solani*. Affected cattle exhibit severe respiratory distress, a rapid respiratory rate, typical extension of the head and neck associated with dyspnea, and frothy exudate around the mouth before death. The disease has been reproduced experimentally in cattle with sweet potatoes artificially inoculated with *F. solani* isolated from moldy sweet potatoes associated with a field outbreak of the disease in Georgia. Although it is uncertain at present whether *F. solani* is involved in etiology of the bovine atypical interstitial pneumonia and whether or not the pulmonary toxins present in moldy sweet potatoes are specific degradation products of *F. solani*, the fact remains that moldy sweet potatoes cause field outbreaks of respiratory disease in cattle. Moreover, these potent lung toxins have been found naturally in sweet potatoes offered for sale in supermarkets in the United States, and they are not destroyed by normal cooking procedures. It is evident that the consumption of moldy sweet potatoes is potentially dangerous to human and animal health (123, 124).

F. MONILIFORME

Currently, *F. moniliforme* is the *Fusarium* species receiving most of the attention from research workers studying mycotoxins. *F. moniliforme* is one of the most prevalent fungi associated with basic human and animal dietary staples such as corn (124, 149). This fungus has been suspected of being involved in human and animal diseases since its original description in 1904 (203). In the early 1900s, widespread field outbreaks of a disease in animals associated with the ingestion of moldy corn occurred in the United States (173). Peters (173) reported that the hooves of cattle and horses sloughed, pigs shed their bristles, chickens lost their feathers, some animals developed convulsions, and a high percentage of affected animals died. *F. moniliforme* was the fungus most commonly associated with moldy corn and was implicated as the cause of the disease "moldy corn toxicosis" (173). In some areas of the world, *F. moniliforme* has been associated with high rates of human esophageal cancer. In southern Africa, the highest rate of human esophageal cancer occurs in the southwestern districts of the Transkei, where corn is the main dietary staple (131). Several strains of *F. moniliforme* isolated from corn produced in these districts have been found to be acutely toxic to ducklings (111). When culture material of these isolates grown on autoclaved corn was fed to experimental animals, the lesions induced included cirrhosis and nodular hyperplasia of the liver and intraventricular cardiac thrombosis in rats, leukoencephalomalacia and toxic hepatosis in horses, pulmonary edema in pigs, nephrosis and hepatosis in sheep, and acute congestive heart failure in baboons (111, 112). When corn-based feed that was naturally contaminated with *F. moniliforme* and was associated with outbreaks of equine leukoencephalomalacia (LEM) was fed to rats, multiple hepatic nodules and pale depressed hepatic areas resulted. Histological examination revealed multiple hepatic neoplastic nodules and large areas of adenofibrosis and cholangiocarcinomas (248). Marasas et al. (122) found that isolate MRC 826 of *F. moniliforme* grown on autoclaved corn and fed at a dietary level of 4% for 286 days and 2% for the rest of the experiment was hepatocarcinogenic. This material caused hepatocellular carcinoma in 80% and ductular carcinoma of the liver in 63% of the rats that survived for more than 450 days.

Mycotoxins Produced by *F. moniliforme*

Moniliformin. The mycotoxin moniliformin was first reported to be produced by an isolate of *F. moniliforme* from corn kernels in the United States (45). This isolate lost the ability to produce moniliformin during the course of a study to determine the structure of the toxin (216). Moniliformin was eventually isolated and chemically characterized from a strain of *F. moniliforme* isolated from millet in Nigeria, and this strain has been reported to produce large amounts of moniliformin (216). However, the strain from millet recently was identified as *F. nygamai* because it produced chlamydospores (127).

In a study of moniliformin production in *Fusarium* section *Liseola* (129), it was found that of 58 strains of *F. moniliforme* from southern Africa, only 13 that were toxic to ducklings produced moniliformin in cultures of autoclaved corn. The other 45 strains that were toxic to ducklings did not produce chemically detectable levels of moniliformin in culture. These 45 toxic strains were isolated from corn in Kenya, South Africa, and Transkei.

There are conflicting reports in the literature regarding the production of moniliformin by cultures of *F. moniliforme*. Overall, only 22% of the toxic strains produced chemically detectable levels of moniliformin, and the mean yield was low (129). In particular, strains of *F. moniliforme* from corn produced small amounts, and only 6 of 51 strains produced moniliformin. Cultures that did not produce moniliformin induced LEM in equine animals. Thus, it appears that *F. moniliforme* generally is a poor producer of moniliformin and that many toxic strains, in particular, those isolated from corn, do not produce moniliformin and that other species of *Fusarium*, such as *F. subglutinans*, are better producers of moniliformin.

Fusarins. Assays of isolates of *F. moniliforme* grown on sterile cracked corn showed that extracts of 21 of 33 isolates were mutagenic for *Salmonella typhimurium* TA100 (25). Most (70%) of the isolates from corn and an isolate from sorghum produced mutagens (25). In 1983, Gelderblom et al. (68), using the *Salmonella* assay, showed that strains of *F. moniliforme* isolated from Transkeian corn produced mutagenic compounds. The *Salmonella* assay subsequently was used as a monitoring system for isolation of mutagenic compounds from cultures of *F. moniliforme* MRC 826. The main mutagenic compound purified from this strain of *F. moniliforme* was identical to fusarin C, a compound independently isolated from a culture of *F. moniliforme* by Wiebe and Bjeldanes (244). Because fusarin C is a mutagenic metabolite of *F. moniliforme*, experiments were carried out to determine the cancer-initiating activity in rats. The results obtained (67) did not support the theory that fusarin C is carcinogenic or has a role in the hepatocarcinogenicity of *F. moniliforme* MRC 826.

Fumonisins. In 1988, Bezuidenhout et al. (20) characterized the structures of fumonisins, a new group of mycotoxins that had been purified from cultures of *F. moniliforme*. Fumonisins B_1, B_2, and B_3 have been isolated and characterized (20, 66, 176, 177). Fumonisin B_1 has cancer-promoting activity in rats (66), causes equine leukoencephalomalacia (103, 121), and is associated with porcine pulmonary edema (82, 194). Fumonisin B_1 production has been demonstrated for several species in addition to *F. moniliforme* and *F. proliferatum* (Matsushima) Nirenberg from widely separated geographic areas (151, 152). These include *F. nygamai* Burgess & Trimboli, *F. anthophilum* (R. Braun) Wollenw., *F. dlamini* Marasas, Nelson & Toussoun, and *F. napiforme* Marasas, Nelson & Rabie (151, 152, 224). Research on the effects of the fumonisins on animal and human health is continuing.

MYCOTOXICOSES ASSOCIATED WITH THE GROWTH OF *F. MONILIFORME* ON CORN

Equine LEM

Equine LEM, a neurotoxic disease of horses, donkeys, and mules, is characterized by liquefactive necrotic lesions in the white matter of the cerebral hemispheres (124). Equine LEM has been referred to as the blind staggers, cerebritis, moldy corn disease, leukoencephalitis, corn stalk disease, encephalomyelitis, foraging disease, and cerebrospinal meningitis (249). This condition, which is seen worldwide, is often characterized pathologically by liquefactive necrosis of the white matter of one or both cerebral hemispheres. Typical clinical signs of intoxication appear abruptly and consist of apathy, somnolent appearance with protruding tongue, reluctance to move backwards, aimless circling, and ataxia. The signs of nervous disorder become more pronounced as time passes, and the animal walks into large stationary objects apparently through lack of comprehension rather than lack of vision. Finally, the animal may become extremely excitable and frenzied, and during this period of delirium it may run wildly into large, stationary objects such as fences. Death may be preceded by recumbency and paddling limb movements. The course of the disease from the onset of clinical signs to death can be extremely rapid (less than 7 h), or it may last several days (123).

In early reports, researchers associated LEM with the ingestion of moldy corn. When equidae were fed corn contaminated with *F. moniliforme*, they died of the disease. In other experiments, when corn cultures of pure strains of *F. moniliforme* were fed to horses, the animals developed LEM (111, 112, 121). Marasas et al. (121) showed that, when horses were dosed by stomach tube with culture material of *F. moniliforme* grown on corn, they developed severe hepatosis and mild edema of the brain. In another experiment, fumonisin B_1 was extracted and purified from culture material of *F. moniliforme*. A horse injected with purified fumonisin B_1 seven times during the first 9 days of an experiment developed clinical signs on day 8 which included nervousness followed by apathy, a wide-based stance, trembling, ataxia, reluctance to move, paresis of the lower lip and tongue, and an inability to eat or drink. The horse was euthanized on the 10th day, and the principal lesions were severe edema of the brain and early, bilaterally symmetrical, focal necrosis in the medulla oblongata (121). In a later experiment, LEM was induced by the oral administration of fumonisin B_1. Two horses were dosed and developed nervous signs such as apathy, changes in temperament, lack of coordination, walking into objects, and paralysis of the lips and tongue. Characteristic lesions of LEM were present in the brains of both horses (103). These two experiments (103, 121) prove conclusively that fumonisin B_1 can induce LEM in horses.

PPE

Pulmonary edema in swine (PPE) caused by feeding *F. moniliforme* MRC 826 propagated on corn in bulk was reported in 1981 (112). Two pigs dosed by feeding bulk culture material in their food ration developed pulmonary edema. The next report on PPE appeared in 1990 (82). It described simultaneous epizootics on two southwest Georgia farms which resulted in the deaths of 34 mature swine. Gross pathological changes observed included extremely marked pulmonary edema and massive hydrothorax. The thoracic cavities were overfilled with golden-yellow liquid. Routine diagnostic testing for toxins and infectious agents failed to

establish an etiology, and these epizootics appeared to represent an unrecognized disease problem (82).

To investigate this disease, feed consisting of corn screenings from the 1989 crop common to both farms where this problem occurred were used (82). Deaths began about 5 days after the screenings were first fed and ceased 24 h after screenings were removed as the feed source. On day 7 of the feeding study, one animal was found dead and a severely dyspneic animal was euthanized on the same day. At necropsy, both animals exhibited marked pulmonary edema and hydrothorax previously seen in field cases. Corn screenings were cultured, and *F. moniliforme* was recovered from samples from both farms. Preliminary data showed that the concentration of fumonisin B_1 ranged from 105 to 155 μg/g in the two feed samples (82). Additional tests with pure fumonisin B_1 and fumonisin B_2 were done on pigs. One pig was injected daily with fumonisin B_1 and died on day 5. This pig developed pulmonary edema and exhibited lesions similar to those observed in field and other experimental cases (82).

During the 1989 corn harvest season, numerous outbreaks of PPE were reported and were generally confined to the central United States (194). In almost all cases, feed containing corn and/or corn screenings from the 1989 harvest was implicated as the causative factor. Because of the 1981 report of a PPE-like syndrome (112), feed samples were collected for mycological evaluation and chemical analyses. Five feed samples associated with PPE cases, primarily corn and/or corn screenings, were obtained from farms in southeastern Iowa. *F. moniliforme* was isolated from all samples, and *F. proliferatum* was isolated from one sample. The isolates of *F. moniliforme* from feed produced fumonisin B_1 in amounts ranging from 900 to 2,350 μg/g and fumonisin B_2 in amounts ranging from 120 to 350 μg/g when grown in corn culture. The single isolate of *F. proliferatum* produced 1,670 μg of fumonisin B_1 and 150 μg of fumonisin B_2 per g when grown in corn culture. These data (194) and the data of Harrison et al. (82) indicate that fumonisin B_1 is probably the cause of PPE.

Ross et al. (194) also examined feed samples obtained during the 1989 corn harvest season. A total of nine feed samples were obtained from farms in southeastern Iowa: two were associated with a case of equine LEM, five were associated with cases of PPE, and two samples were not associated with animal health problems. All samples were primarily corn and/or corn screenings. *F. moniliforme* was isolated from all nine samples, and *F. proliferatum* was isolated from one LEM sample, one PPE sample, and one nonproblem sample. All of the isolates of *F. moniliforme* and *F. proliferatum* produced fumonisins in corn cultures in amounts ranging from 960 to 2,350 μg/g, suggesting that the potential exists for fumonisin contamination in any feed containing these two species.

Experimental Liver Cancer

Kriek et al. (111) isolated 21 strains of *F. moniliforme* (*F. verticillioides*) from crops of corn in South Africa and the Transkei. These strains did not produce moniliformin, and the majority were toxic to ducklings. Acute mortality was common in ducklings fed corn culture material of these isolates. In rats fed this material, the mean time to death was at least 24 days even with the most toxic isolate. Cirrhosis and nodular hyperplasia of the liver and acute and proliferative endocardial lesions with concurrent intraventricular thrombosis were encountered frequently (111). In a later study (122), culture material on corn of *F. moniliforme* MRC 826 was fed to rats on a lifelong basis. At a dietary level of 8%, culture material was hepatotoxic and caused 100% mortality. Hepatic lesions in rats that died were characterized by cirrhosis, nodular hyperplasia, and bile duct proliferation. At lower dietary levels, culture material was hepatocarcinogenic and caused hepatocellular carcinoma and ductular carcinoma of the liver. No hepatocellular or ductular carcinomas occurred in the control animals. Hepatocellular carcinomas in the experimental rats invariably developed in severely cirrhotic livers showing nodular hyperplasia. Adenofibrosis developed concurrently with hepatocellular carcinoma (122).

In other experiments (155, 248), corn that was being fed during an epizootic of LEM was obtained from a farm in which 9 of 15 horses died. Clinical and neuropathological lesions were consistent with the diagnosis of LEM. The locally grown corn, which was not treated with fungicide, was ground finely and fed unsupplemented to rats. The predominant species recovered from this corn was *F. moniliforme*. Analysis of the feed for aflatoxins at the <0.9-ppb level was negative. Control animals euthanized and evaluated on day 176 were free of significant gross lesions. Gross lesions in all test rats necropsied from 123 to 176 days postfeeding were confined to the liver and consisted of multiple hepatic nodules and pale depressed hepatic areas. Histological examination revealed multiple hepatic neoplastic nodules and large areas of adenofibrosis and cholangiocarcinomas. This study was the first to report on the hepatocarcinogenicity of a sample of equine feed infested with *F. moniliforme* (155, 248).

Gelderblom et al. (65) fed a corn-based diet containing 50 μg of partially pure (not less than 90%) fumonisin B_1 per g, isolated from culture material of *F. moniliforme* MRC 826, to a group of 25 rats over a period of 26 months. A control group of 25 rats received the same diet without fumonisin B_1. The liver was the main target organ in fumonisin B_1-treated rats, and the hepatic pathological changes were identical to those previously reported in rats fed culture material of *F. moniliforme* MRC 826. All fumonisin B_1-treated rats that died or were killed from 18 months onward suffered from a micro- and macronodular cirrhosis and had large expansile nodules of cholangiofibrosis at the hilus of the liver. Ten of 15 fumonisin B_1-treated rats (66%) that were killed and/or died between 18 and 26 months developed primary hepatocellular carcinoma, and metastases to the heart, lungs, or kidneys were present in 4 of the rats. No neoplastic changes were observed in any of the control rats. Chronic interstitial nephritis was present in the kidneys of fumonisin B_1-treated rats killed after 26 months. No neoplastic changes were observed in the esophagus, heart, or forestomach of fumonisin B_1-treated rats, which was contrary to previous findings when culture material of the fungus was fed to rats (122). It was concluded that fumonisin B_1 is responsible for the hepatocarcinogenic and the hepatotoxic, but not all of the other toxic, effects of culture material of *F. moniliforme* MRC 826 in rats (65).

Esophageal Cancer

In Africa, the highest human esophageal cancer rate occurs in the southwestern districts of the Transkei, while the rate in the northeastern region of the Transkei is relatively low (124, 130, 131). Corn is the main dietary staple in both areas. In a comparative study of the mycoflora of home-grown corn produced in the two areas, the most striking and consistent difference was the significantly high incidence of *F. moniliforme* in corn produced in the area with a high rate of cancer (122, 130, 222). Esophageal carcinoma as it occurs in nature has not been induced in animals with cultures of *F. moniliforme*, and consequently there is no experimental proof of a causative relationship.

In China, *F. moniliforme* is one of the fungi most frequently associated with foodstuffs in Lin Xian county in Henan Province, which is one of the highest-risk areas for esophageal cancer in the world (122). According to Yang (258), cornmeal inoculated with isolates of *F. moniliforme* from Lin Xian county has been found to induce tumors in several different organs in rats (122). Although carcinoma of the esophagus as it occurs in nature was not observed, the *F. moniliforme*-infected cornmeal induced epithelial hyperplasia, precancerous changes, and papillomas of the esophagus and stomach of rats and mice (122).

At present, it is not possible to postulate a causative role for *F. moniliforme* in the etiology of human esophageal cancer because there is no direct experimental evidence of a cause-and-effect relationship. However, the finding that the incidence of *F. moniliforme* in corn is correlated with the esophageal cancer rate in Transkei (131) and the frequent association of *F. moniliforme* with foodstuffs in areas of China (258) with higher rates merit further investigation of the possible role of *F. moniliforme* in the etiology of human esophageal cancer (122).

Distribution of *Fusarium* Species That Produce Fumonisins

Much of the early work on production of fumonisins was done with *F. moniliforme* MRC 826. However, recent testing has shown that other strains of *F. moniliforme* as well as other *Fusarium* species also produce these mycotoxins. Thiel et al. (224) tested *F. decemcellulare* Brick, *F. sporotrichioides*, *F. poae*, *F. tricinctum* (Corda) Sacc., *F. avenaceum*, *F. semitectum*, *F. camptoceras* Wollenw. & Reinking, *F. equiseti*, *F. acuminatum* Ell. & Ev., *F. scirpi* Lambotte & Fautr., *F. longipes* Wollenw. & Reinking, *F. sambucinum* Fuckel, *F. graminearum*, *F. reticulatum* Mont., *F. compactum* (Wollenw.) Gordon, *F. lateritium*, *F. moniliforme*, *F. proliferatum*, *F. subglutinans*, *F. anthophilum*, *F. oxysporum*, *F. nygamai*, and *F. napiforme*. Of the species tested, only *F. moniliforme*, *F. proliferatum*, and *F. nygamai* produced fumonisins. In another study, Nelson et al. (151) tested strains of *F. moniliforme* from various substrates and geographic areas for production of fumonisin B_1. They tested strains from corn-based feed from the United States; from millet and sorghum in Nigeria and Zimbabwe; from corn kernels from Nepal; from sorghum stalks and grain, corn, sugarcane, and soil from Australia; from good-quality corn for use in poultry rations in the United States; and from corn silks from Iowa and strains associated with mycotic keratitis and various types of cancer in humans from the United States and Canada. They considered those strains that produced up to 50 ppm of fumonisin B_1 to be low producers, those producing 50 to 500 ppm to be intermediate producers, and those producing >500 ppm to be high producers. Most of the strains from corn-based feed associated with LEM were high producers (16 of 20), whereas fewer strains from millet and sorghum were high producers (4 of 15) and a number of strains did not produce the compound. Only one strain from corn kernels from Nepal was a high producer (1 of 10), most strains from good-quality corn for poultry rations were high producers (7 of 8), and the strains from corn silks were mainly high producers (8 of 9). All strains from sorghum stalks and grain, corn, sugarcane, and soil from Australia were nonproducers (10 of 10). Several of the strains from humans (9 of 13) were high producers.

In another study, Nelson et al. (152) tested species other than *F. moniliforme*, including *F. proliferatum*, *F. subglutinans*, *F. anthophilum*, *F. beomiforme* Nelson, Toussoun & Burgess, *F. dlamini*, *F. napiforme*, and *F. nygamai*. They found that 17 of 31 strains of *F. proliferatum* were high producers, 1 of 17 strains of *F. anthophilum* was a high producer (and 2 of 17 strains were low producers), 5 of 9 strains of *F. dlamini* were low to intermediate producers, 5 of 31 strains of *F. napiforme* were low to intermediate producers, and 6 of 27 strains of *F. nygamai* were high producers. *F. subglutinans* and *F. beomiforme* did not produce detectable amounts of fumonisin B_1. These results indicate that the potential for production of fumonisins in natural substrates and agricultural commodities exists in strains from a variety of substrates and geographic areas. Of the species tested, *F. moniliforme*, *F. proliferatum*, *F. nygamai*, and *F. napiforme* are probably the most important producers of fumonisin B_1 because of their association with food grains such as corn, millet, and sorghum and with animal mycotoxicoses such as equine LEM and PPE.

INFECTIONS CAUSED BY *FUSARIUM* SPECIES

Introduction

As described earlier, *Fusarium* species are soilborne fungi that are distributed worldwide and are known to be plant, animal, and human pathogens. *Fusarium* spp. can affect humans by producing either mycotoxicosis or invasive disease. For example, alimentary toxic aleukia is a mycotoxicosis that caused the death of hundreds of thousands of people in Russia at the close of World War II (124). This disease affects the hematopoietic system and develops after the ingestion of overwintered cereal grains colonized with *F. sporotrichioides* and *F. poae* (96, 124). The toxin produced by these organisms is called T-2 toxin. Invasive fusariosis in humans requires two factors for development: exposure to the pathogen and some degree of local or systemic impairment of the host defenses.

Fusarium spp. have been recovered in different areas of all five continents (28, 32). Although they are often regarded as soilborne, wind and rain could play an important role in the dissemination of these fungi. Circumstantial evidence of wind dispersion of *Fusarium* spores as far as 400 km has been reported (165). A survey of airborne fungi carried out in the United States indicated that *Fusarium* spp. were more frequently present in air samples than were *Aspergillus* spp. (39).

Wind dispersal may explain the isolation of *Fusarium* spp. from 17% of throat specimens of 27 nonhospitalized healthy adults, primarily medical school students (44). The presence of high levels of antibodies to extracellular polysaccharides of molds in the sera of 125 healthy subjects indicates that healthy humans are frequently in contact with the fungal extracellular polysaccharides, presumably by inhalation (157). *Fusarium* spp. have also been isolated from the flora of the conjunctival sac (11) with an incidence that correlated with the number of airborne fungi in the environment.

Disseminated invasive fusariosis was first reported in 1973 (42). Since then, several other cases and a few small series of systemic fusarial hyalohyphomycosis in immunosuppressed patients have been reported (1, 6, 8, 26, 63, 106, 132, 137, 140, 144, 145, 147, 161, 169, 187, 189, 219, 230, 232, 234, 243, 263, 265), with a significant increase being noted recently. Localized or systemic fusarial infections have been reported from all around the world (Fig. 23). Over the last 10 years, the Fusarium Research Center at The Pennsylvania State University, University Park, has received 208 cultures representing 11 different *Fusarium* species isolated from patients with fusarial hyalohyphomycosis.

The following will focus on the experimental infection, pathogenesis, clinical manifestations, treatment, and outcome of infections caused by *Fusarium* spp.

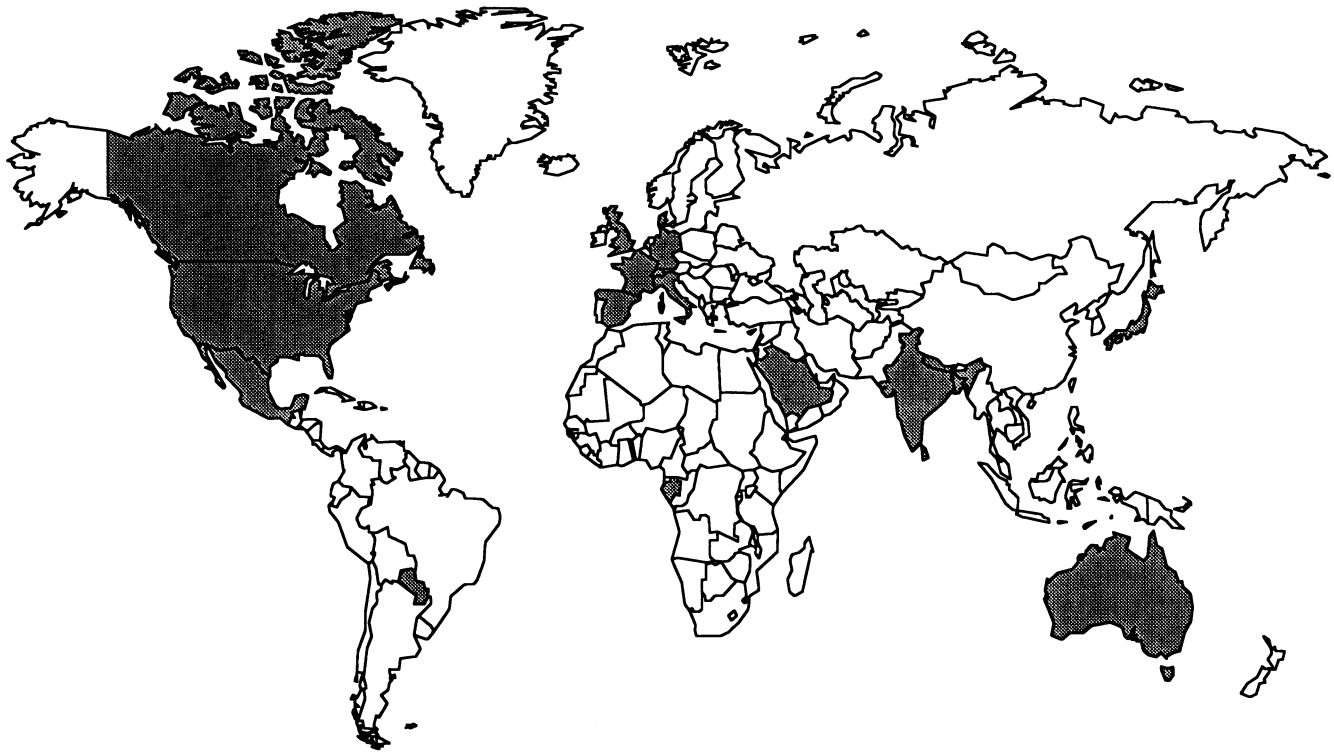

FIG. 23. Countries where cases of *Fusarium* infections in humans have been reported. Countries marked are Canada, United States, Mexico, Paraguay, Spain, France, England, Denmark, Switzerland, Germany, Italy, Gabon, Saudi Arabia, Israel, Nepal, India, Sri Lanka, Bangladesh, Australia, and Japan.

PATHOGENESIS OF INFECTION

Experimental Infections

Ocular infection. Because of the emergence of *Fusarium* spp. as significant ocular pathogens in humans (50, 88, 105, 139, 174, 221, 230, 235, 246), several attempts have been made to establish animal models of infection. A short-lived infection that could not be maintained for more than a few days was reported by Jones et al. in rabbits (99). Forster and Rebell (58) showed that pretreatment with corticosteroids resulted in a more prolonged but still self-limiting disease. In general, the use of corticosteroids has always been needed to sustain otherwise transient infection in the cornea of rabbits. Kiryu (107) showed that in the dexamethasone-treated cornea of rabbits the neutrophils could not ingest and destroy the fungi and that a hypha-in-hypha structure developed. These events were not seen in the absence of dexamethasone treatment. Burda and Fisher (31) developed a fusarial corneal infection model in rats. An increased rate of infectivity was observed with steroid pretreatment. Finally, O'Day et al. (159) developed a rat model of fulminant ocular infection culminating in endophthalmitis that resembled remarkably that encountered in humans. *F. solani* was the infectious agent, and infection could be established and maintained without the need for immunosuppression. In this model, the inoculum was injected into the anterior chamber of the eye, in contrast to previous experiments in which the corneal route of inoculation was used.

Brain infection. Twenty-four-day-old chicks were inoculated intracerebrally with a broth culture of *Fusarium* spp. The animals developed incoordination, labored breathing, torticollis, and inability to feed within 48 h, and an 80% mortality was observed in 7 days. The histological findings revealed the presence of septate fungal hyphae and macroconidia accompanied by necrosis, endothelial proliferation, neuronal degeneration, gliosis, and demyelinization in the cerebrum of these chicks (2). It is not clear whether the disease induced by direct intracerebral inoculation was an infection or the result of toxin production by the inoculated *Fusarium* sp.

Disseminated infection. Oral inoculation of *Fusarium* spp. in 24-day-old healthy chicks did not result in disseminated infection. Intranasal inoculation of *Fusarium* spp. caused disseminated infection to brain, liver, and air sacs. However, no mortality was observed (2). Legrand et al. established a murine model of lethal disseminated fusarial infection (115). *F. solani* conidia were injected intravenously into healthy and immunosuppressed CF1 mice, leading to a 100% mortality. Survival was correlated with inoculum size, as mice injected with the higher inocula had shorter survival times. Neutropenia was also associated with shorter survival, absence of tissue inflammatory cellular reaction, and persistent disseminated infection. Histopathologic findings were similar in many respects to those seen in human infections: presence of necrotizing abscesses, acute branching septate hyphae, and neutrophil and macrophage infiltration. Endovascular invasion and thrombosis were also found. This reproducible murine model is currently used to study the pathogenesis of murine fusarial infections.

An interesting feature of *Fusarium* spp. is their ability to disseminate into the bloodstream, resulting in a high rate of isolation from blood culture specimens. The rate of isolation for other opportunistic molds, particularly *Aspergillus* spp., is very low (6). In order to understand this phenomenon, an animal model that would allow frequent sampling of adequate volumes of blood was needed; hence, a rabbit model of

TABLE 1. Human diseases caused by toxigenic *Fusarium* species

Disease	*Fusarium* sp.	Toxin[a]	Source	Country	Reference
ATA[b]	*F. sporotrichioides*	T-2	Overwintering harvested grains	USSR	95
Kashin-Beck disease[c]	*F. poae*	??		N. Korea, N. China	125
Akakabi-byo[d]	*F. graminearum*	NVL	Cereal grains	Japan	125
	F. sporotrichioides	DONL, etc.			
?Gastrointestinal disorder	*Fusarium* sp.	DONL, NVL, T-2, ADONL	Bread from moldy wheat	Kashmir Valley, India	21
?Anomalous sexual development	*Fusarium* sp.	Estrogenic mycotoxin	Meats and poultry products	Puerto Rico	171
Keshan disease[e]	*F. moniliforme*	Moniliformin	Corn seeds	China	267
?Esophageal cancer	*F. moniliforme*	Fumonisins	Corn	South Africa	222

[a] NVL, nivalenol; DONVL, deoxynivalenol; ADONVL, acetyldeoxynivalenol.
[b] ATA, alimentary toxic aleukia (gastrointestinal symptoms followed by pancytopenia).
[c] Dystrophic osteoarthrosis involving peripheral joints in children.
[d] Gastrointestinal disorder.
[e] Endemic myocardiomyopathy.

infection with this pathogen was developed (7). Rabbits were pretreated with daily doses of triamcinolone and repeated intravenous doses of cyclophosphamide. Intravenous inoculation of *F. solani* conidia resulted in disseminated infection that was repeatedly documented by its isolation from blood cultures.

Determinants of Virulence of *Fusarium* spp.

Fusarium spp. are opportunistic fungi that can cause life-threatening infections, mainly in immunocompromised hosts. While the particular susceptibility of the host is a major determining factor in the establishment of the infection, it is also clear that *Fusarium* spp. possess several cellular and molecular attributes that, together, may confer different degrees of inherent virulence on these organisms. The combination of these virulence factors and the immunocompromised status of the host contribute to the development of invasive fusarial infections. Toxins, enzyme production, and adherence to prosthetic materials have all been postulated as virulence factors for *Fusarium* spp.

***Fusarium* mycotoxins.** Mycotoxin production by *Fusarium* spp. has been reviewed earlier. We shall discuss here the potential role of these mycotoxins in the pathogenesis of human disease. The best example is alimentary toxic aleukia, which has been associated with the ingestion of overwintered cereal grains colonized by the toxigenic *F. sporotrichioides* and *F. poae* (13, 93–95, 124, 141, 206, 229). The toxin produced by these organisms (called T-2 toxin) has been shown to be the principal component responsible for the acquisition of alimentary toxic aleukia. A. Z. Joffe states that "T-2 toxin was the principal component responsible for the fatal incidents of ATA [alimentary toxic aleukia]." He also mentioned that all syndromes of alimentary toxic aleukia have been well documented in test animals (95). Other human disorders and their possible association with *Fusarium* mycotoxins are summarized in Table 1. The trichothecenes (e.g., T-2 toxin, nivalenol, deoxynivalenol, and acetyldeoxynivalenol) are potent inhibitors of eukaryotic protein synthesis (135), and the target organs include actively dividing tissues such as bone marrow, lymph nodes, spleen, thymus, and intestinal mucosa (93, 237). In vitro, T-2 toxin has been shown to have cytostatic (142) potential, to inhibit platelet aggregation (259), and to increase the prothrombin time (48). Experimental injection of T-2 toxin to rats resulted in cardiomyopathy (260).

In addition, the trichothecene toxins inhibit the immune system. In vitro, they impair cellular immunity and decrease the humoral response to T-dependent antigens (172, 192). In vivo, they increase the skin graft rejection time (193) and the susceptibility to candidiasis (199), cryptococcosis (62), herpes simplex virus infection (61), listeriosis (172), and salmonellosis (236). The target cells are the lymphocytes and macrophages, but the former seem to be the more susceptible ones. The possibility that trichothecene action on lymphocytes is mediated by a receptor has been suggested (172).

The estrogenic metabolite zearalenone decreases the resistance to listeriosis in mice (172). Table 2 summarizes the effect of *Fusarium* mycotoxins on the immune system. Recently, Visconti et al. (238) evaluated the in vitro cytotoxicity of 23 *Fusarium* mycotoxins on cultured human cell lines and their inhibitory effect on proliferation of phytohemagglutinin-stimulated human peripheral blood lymphocytes. T-2 toxin was the most cytotoxic, followed by other trichothecenes. The nontrichothecene toxins were the least cytotoxic.

The fumonisins (known as B_1, B_2, B_3, B_4, etc.) are structur-

TABLE 2. Effect of *Fusarium* mycotoxins on the immune system

Toxin	Effect[a]	Reference
T-2 toxin	Cytostatic	142
	↓ Proliferation and function of lymphocytes	238
	↓ Protein synthesis and ↓ phagocytosis by macrophages	69
	↓ Resistance to candidiasis	199
	↓ Resistance to cryptococcosis	62
	↓ Resistance to herpes simplex virus	61
	↓ Resistance to salmonellosis	236
	↓ Chemotaxis of neutrophil	261
Deoxynivalenol	↓ No. of lymphocytes	57
	↓ No. of monocytes	57
	↓ Immunoglobulin M	57
	↑ Immunoglobulin A	57
	↓ Delayed-type hypersensitivity	172
	↓ Humoral response to T-dependent antigens after 3 wk	172
Zearalenone	↓ Resistance to listeriosis	172
Fumonisin B_1	↓ Phagocytic function of macrophages	179

[a] ↓, Decrease.

ally similar to the long-chain (sphingoid) base backbones of sphingolipids and are known to inhibit sphingolipid synthesis (262). This event seems to be the first step in the pathogenesis of cellular toxicity, which may result in brain, pulmonary, and liver damage in animals and cause equine LEM (240), liver cancer in rats (156), and PPE (83). Fumonisins were shown to cause significant reduction in the phagocytic potential of chicken peritoneal macrophages after 4 h of in vitro exposure to the toxin (179).

Fusarium toxins could also play an important role in the pathogenesis of skin infections. Dermal toxicity of *Fusarium* toxins T-2, diacetoxyscirpenol, fusarenon, and butenolide were evaluated individually and in combination on the shaved skin of guinea pigs. Erythema and induration were observed on skin patches treated with the toxins. These findings correlated histologically with the thickening of stratum malpighii, mild to moderate degeneration of fibrocytes, and cellular infiltration (22).

All *Fusarium* mycotoxin effects seem to be dose dependent and reversible (83, 238, 250, 262). This raises the possibility that toxin production in humans with fusarial infections may play a role in the establishment and persistence of fusarial infections, particularly in patients who are already immunocompromised. It is important to note, however, that mycotoxin production by *Fusarium* species causing invasive hyalohyphomycosis in human tissue has not been demonstrated.

Enzyme production. Definitive evidence linking enzyme production to the virulence of *Fusarium* species is lacking. In vitro production of proteases by *F. solani* and of collagenases by *F. moniliforme* has been documented (100). Whether these enzymes play a role in the pathogenesis of human infections remains to be determined. On the basis of electron microscopy findings, Kiryu (107) suggested that these enzymes might have a role in the pathogenesis of fusarial keratitis.

Adherence to prosthetic material. The ability of *Fusarium* species to adhere to silastic catheters has been reported. McNeely et al. (136) were the first to demonstrate by electron microscopy that *Fusarium* species invaded the silastic catheter wall of continuous ambulatory peritoneal dialysis (CAPD) catheters and occluded the catheter. Kerr et al. (104) reported on a patient with *Fusarium* peritonitis who was undergoing CAPD. Electron micrographs showed that fungi were adherent to but had not invaded the silastic catheter wall. At our institution, we observed by electron microscopy the invasion and destruction of the wall of a silastic intravenous catheter by *F. oxysporum* (180). This catheter belonged to a patient with catheter-related fusarial fungemia.

Contact lenses (especially soft contact lenses with high water content) can harbor *Fusarium* spp. (196). Approximately 14% of soft contact lenses in asymptomatic lens wearers are colonized with fungus (175). Laboratory studies have confirmed the ability of fungi to adhere, penetrate, and proliferate within the interior matrix of the contact lens (205, 257). Therefore, *Fusarium* spp. are able to colonize and sometimes invade foreign bodies such as contact lenses and silastic catheters, but the ability to colonize host superficial and organ surfaces has not been thoroughly studied. A few reports have mentioned saprophytic colonization of skin ulcers (114), burn scars (18), and a traumatic wound (158). It is conceivable, however, that the ability to colonize tissues could be a major virulence factor for *Fusarium* spp.

Host Response to Infection

The interaction of the immune system with *F. solani* was examined in our laboratory. We concluded that granulocytes and macrophages play essential roles in the immune defense against fusariosis. Macrophages inhibit germination of conidia and growth of hyphae, while granulocytes inhibit only hyphal growth (9).

CLINICAL SPECTRUM AND MANAGEMENT

Foreign-Body-Associated Fusarial Infection

Keratitis in contact lens wearers. Fungi are not part of the normal ocular flora (247), even during contact lens wear (40), but they frequently contaminate contact lens paraphernalia or the lens itself (49, 205). *Fusarium* spp. have been cultured from soft contact lenses during use (205). It has been postulated that after an initial period of attachment fungal products may degrade hydrophilic polymers and hence, allow fungal invasion and multiplication within the interior matrix of the lens (205). Fungal keratitis may occur in 4 to 27% of contact lens wearers depending on the type of lenses (245), and *Fusarium* spp. have been reported in several cases (102, 218, 245).

The most frequently noted predisposing factor for keratitis was improper lens care, which led to contamination of contact lens paraphernalia (245). Aerosolization of conidia, particularly in windy conditions, may also lead to contamination of the lens during use. An additional risk factor includes the presence of a pathologic corneal condition such as a herpes simplex keratitis, accompanied by a chronic epithelial defect, and concomitant local corticosteroid and antibacterial medication (245). Removal of the contaminated lens in addition to topical treatment with natamycin should be part of the therapeutic regimen. Prevention of contact lens-related keratitis includes avoidance of moldy environments and of nonsterile or reusable cleaning solutions. In addition, handwashing before lens manipulation and frequent cleaning and sterilization of the lens paraphernalia are also recommended (245).

Peritonitis following CAPD. Seven patients with fusarial peritonitis following CAPD were reported from five different institutions (41, 104, 136, 189, 264). The clinical presentation was insidious, with fever, abdominal pain, and decreasing drainage from the peritoneal catheter. The peritoneal fluid was cloudy in most of these patients. The outcome was uniformly good after removal of the catheter alone or in combination with antifungal therapy. One patient had persistently positive *Fusarium* cultures of her dialysate fluid for almost a year and progressive occlusion of the cannula lumen by the "fungal vegetation" but no clinical symptoms of peritonitis (104). Fungi growing in the lumens of the catheters were either plugging the pores of the catheter or invading it.

Catheter-associated fungemia. Catheter-associated fungemia caused by *F. chlamydosporum* was reported in a patient with lymphocytic lymphoma (106). We have also recently cared for a patient with catheter-related fusarial infection (180). Electron microscope studies of the central venous catheter revealed plugging of the catheter with masses of fungal hyphae and also showed invasion and destruction of the catheter wall.

All patients with peritoneal or central venous catheter-associated fusarial infections recovered uneventfully when the catheter was removed. In cases of bloodstream infections, antifungal chemotherapy was also instituted. Of note is that all of these patients either had a normal peripheral neutrophil count or had suffered only transient episodes of neutropenia. While these infections cannot be considered localized, the overall good outcome can be attributed to the lack of tissue invasion and the presence of a potential removable focus of infection.

Given the absence of reports of fusarial infections associated with devices made of hard materials (titanium and platinum)

such as artificial heart valves or hip prostheses, and despite the very large number of patients with such implants, the size or the adherence properties of *Fusarium* spp. may not allow them to attach to prostheses made of such hard materials.

Single Organ Invasion

***Fusarium* keratitis.** *Fusarium* spp. (especially *F. solani*) are the most frequent cause of fungal keratitis in the United States (47, 101). Predisposing factors include corneal trauma due to implantation of vegetable or soil matter in patients engaging in outdoor activities (139, 235), preexisting allergic conjunctivitis (230), the use of hydrophilic contact lenses (205) for prolonged periods, and possibly the topical use of corticosteroids and antibacterial eye drop medications (230, 245). The clinicopathological features and diagnosis of fusarial keratitis are similar in many regards to those of fungal keratitis caused by other organisms. Topical natamycin is the treatment of choice given its excellent antifusarial activity in vitro (186, 195), its corneal penetration (160), and its safety profile (191). Silver sulfadiazine has been shown to be active against fusarial keratitis (230). One case of *F. moniliforme* keratitis was successfully treated with cyclopiroxolamine (50). However, fusarial keratitis is relatively resistant to treatment with azoles when compared with the early and fast response of keratitis caused by *Aspergillus* spp. (56, 184, 225). If therapy is delayed, fusarial keratitis may progress to endophthalmitis (174). Fusarial endophthalmitis may result from infection initiated from exogenous or endogenous sources. Exogenous sources include extension of fungal corneal ulcer (which can precede the development of endophthalmitis by 2 weeks to 5 months) and surgical or nonsurgical trauma (174). Endogenous infection may result from hematogenous spread of the fungus from another site of infection in the body (116). Rapid and accurate diagnosis of endophthalmitis is essential if vision is to be salvaged, but in most reported cases patients have had a poor visual outcome (174).

Onychomycosis. Rush-Munro et al. (197) reported on several cases of onychomycosis caused by *F. oxysporum* which tended to cause highly characteristic milky lesions on great toenails. The earliest sign is a white spot at the base of the nail or an extension proximally of the free border. With more advanced infection, the area of nail affected increases, occasionally in a patchy fashion but mostly as a regular extension up or down the nail. There may be onychogryposis, and in a few patients, the whole toenail becomes opaque, distinctly milky white, and thickened at the free border. Ultimately, destruction of part or the entire nail may ensue. While most infections are asymptomatic, swelling and tenderness at the base of the nail may occur. Some patients may seek advice for cosmetic reasons. In the reported series, *F. oxysporum* was more frequently encountered than other filamentous fungi. It has been postulated that *Fusarium* spp. invade great toenails after soil contamination, particularly in people who tend to walk in open sandals or barefooted. Trauma to the great toenail and accumulation of debris in the lateral folds will introduce the organism. Similar findings were noted in a recent series by Velez and Diaz (233). *F. oxysporum* penetrates and invades the keratinous part of the nail plate and the hair shaft (241). Although onychomycosis by *Fusarium* spp. usually behaves as a localized infection in immunocompetent individuals, it could also represent the portal of entry leading to disseminated fusarial infection in immunocompromised patients (72) (Fig. 24). A spreading cellulitis of the great toe is usually present. Treatment includes removal of the infected keratin and topical or systemic antimycotic therapy (197).

Skin infections. *Fusarium* spp. have a propensity to invade skin structures both directly and through the bloodstream. Following initial colonization, localized cutaneous infections develop in the presence of certain predisposing factors such as excessive moisture (52, 53), burn (18), trauma (228), and immunosuppression (19, 52, 263). Several types of clinical lesions have been noted on the skin, including granulomas (19, 215), ulcers (114), necrosis (18), pustules (46), vesicles (228), painful nodules (263), mycetomas (17, 86, 188), and panniculitis (170).

An apparently healthy, 16-year-old Sri Lankan girl developed extensive subcutaneous granulomatous lesions due to *F. oxysporum* (12). These lesions had started almost at infancy and had failed to respond to topical therapy. A combination of ketoconazole and fluorocytosine resulted in marked improvement. The most recent reported case of mycetoma responded to long-term administration of ketoconazole (17). During a 10-year period, *Fusarium* and *Aspergillus* spp. were the most common etiologies of fungal burn wound infections (18).

Otitis. One case of external otitis caused by *Fusarium* spp. was reported among a series of 83 cases of mycotic external otitis in Central Africa. Washing of the ear followed by topical econazole and amphotericin B was effective in eradicating the infection (109).

Bone and joint infections. The first reported case of *Fusarium* osteomyelitis is that of a 7-year-old boy who fell and punctured his knee with a thorn (30). Three weeks later, the diagnosis of fusarial osteomyelitis of the tibia was made. The patient recovered completely after surgical drainage and intravenous amphotericin B therapy. Two other cases of *Fusarium* osteomyelitis were reported in two healthy patients: following surgery in one (167) and trauma in the other (158). Both were receiving broad-spectrum antibacterial agents at the time of the infection. Successful outcome was achieved after surgical debridement and local administration of amphotericin B. In one of these cases (158), a concurrent case of wound colonization by *Fusarium* spp. was reported in another patient in the same ward and nosocomial spread was suggested. Septic arthritis caused by *Fusarium* spp. has been reported in two patients (81, 91). The infection developed after trauma and responded to surgical intervention and amphotericin B.

Invasive intranasal infection. Invasive intranasal *F. oxysporum* infection occurred in a 58-year-old diabetic woman with metastatic sigmoid adenocarcinoma. The clinical presentation was suggestive of rhinocerebral zygomycosis. Biopsy and culture of the internasal scar led to the diagnosis (231).

Brain abscess. A patient with chronic mononucleosislike illness associated with Epstein-Barr virus developed a fatal fusarial brain abscess (217).

Pneumonia. A 5-year-old boy with dysmyelopoietic syndrome developed *F. moniliforme* pneumonia after receiving induction chemotherapy. He was probably exposed to conidia of *Fusarium* spp. while harvesting wheat (266). The patient responded to a total dose of 47 mg of amphotericin B per kg and right lower lobe lobectomy; several other cases of lung involvement were reported in the setting of disseminated fusariosis (26, 243, 265).

Disseminated Multiorgan Infection

Disseminated infections have occurred mainly in cancer patients undergoing intensive chemotherapy or bone marrow transplantation. Since the first description of disseminated fusarial infection in an immunocompromised host in 1973 (42), a significant increase in the incidence of disseminated fusarial infections has been recognized in humans.

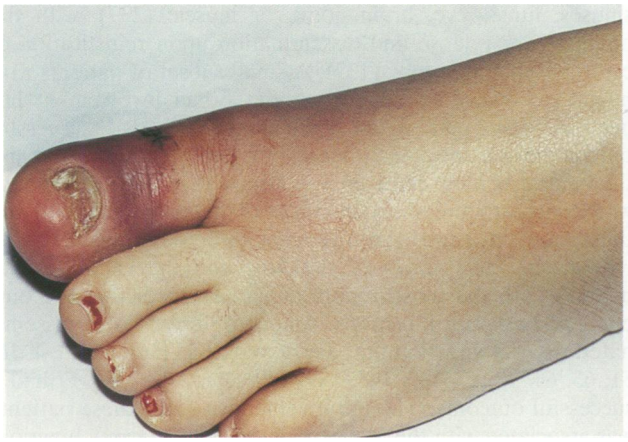

FIG. 24. Onychomycosis by *Fusarium* sp. as the portal of entry in a patient with lymphoma who developed disseminated fusariosis.

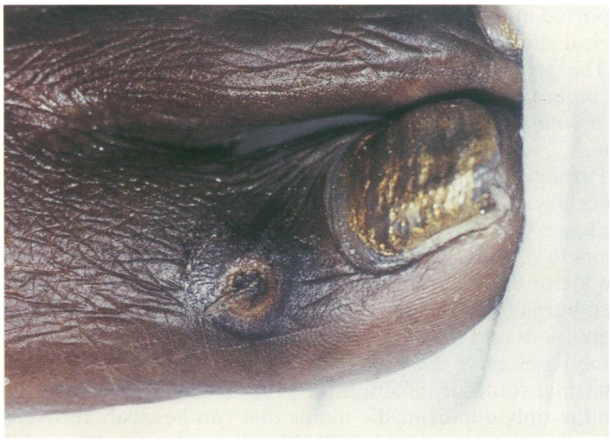

FIG. 26. Necrotic lesion caused by *Fusarium* spp.

Epidemiology. Cases of disseminated infections have been reported from all continents except Africa, even though contamination of cereal samples by *Fusarium* spp. does occur on the African continent (202). In the United States reports of disseminated *Fusarium* infections have come from all parts of the country (31).

While infections may be seen throughout the year, they are more likely to occur during rainy seasons. It has been previously established that wind and rain dispersal of *Fusarium* conidia is a very effective method of spreading the fungus (165).

Disseminated fusarial infections appear to be community acquired. Repeated attempts to isolate a common reservoir in our institution have failed. It is likely that *Fusarium* spp. colonize patients prior to hospital admission. Subsequent immunosuppression and neutropenia could then result in infection. On the other hand, Summerbell et al. (220) have cultured *Fusarium* spp. from potted plants in hospitals, and Nuovo et al. (158) have reported on nosocomial transmission of *Fusarium* spp. in two patients with wound infection. However, environmental cultures conducted at our institution failed to yield *Fusarium* spp. Consequently, we believe that most *Fusarium* infections are likely to be community acquired.

At least 58 patients with disseminated fusarial infections have been reported (3, 4, 16, 18, 51, 63, 64, 72, 87, 119, 143, 145, 161, 181, 189, 190, 198, 201, 219, 237). The median age of these patients was 32 years, with a range of 2 to 69 years. The male-to-female ratio was 2.6:1, without apparent predilection for race. The majority of these patients had acute leukemia as underlying disease, while a few patients had either chronic leukemia, aplastic anemia, lymphoma, or extensive burns. In additional single case reports, the underlying diseases included multiple myeloma, heat stroke, myelodysplastic syndrome, neuroblastoma, and metastatic melanoma following autologous bone marrow transplantation. Nineteen patients had undergone bone marrow transplantation (allogeneic in 13 cases and autologous in 6). Most patients were receiving antifungal prophylaxis with ketoconazole, oral nystatin, or even amphotericin B at the time of the infection. In one case, disseminated fusariosis developed while the patient was receiving alternate-day antifungal treatment with amphotericin B and daily rifampin and fluorocytosine (16). The common risk factor in this patient population seems to be immunosuppression, particularly neutropenia. Impaired neutrophil function is probably important in patients with extensive burns or those suffering heat stroke. In such patients, the thermal injury appears to interfere with the complement system and the activity of neutrophils (84).

Although most infections occurred in patients with active underlying disease, recently an episode of disseminated fusariosis with heavy involvement of liver and lungs has been

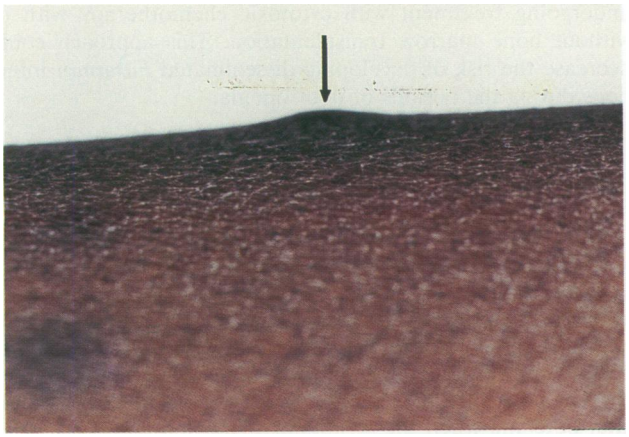

FIG. 25. Subcutaneous nodule caused by *Fusarium* spp.

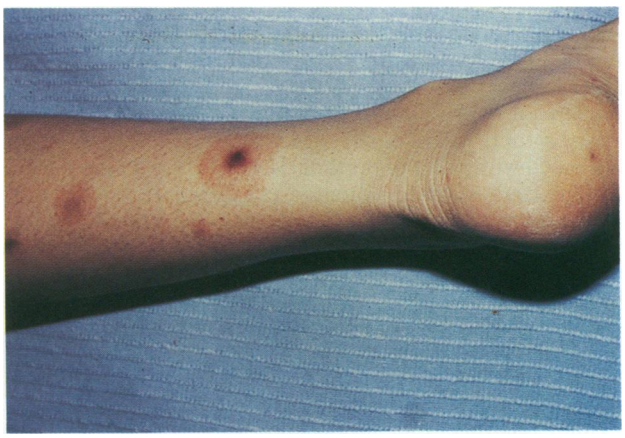

FIG. 27. Characteristic target lesion caused by *Fusarium* spp.

reported in an apparent healthy farmer, although no immunological studies were done (119).

The species of *Fusarium* implicated in disease include *F. solani* in almost half of the cases, followed by *F. oxysporum* and *F. moniliforme*. Several other species have also caused infection.

Pathogenesis. Two modes of acquisition of the infection seem likely: (i) respiratory, following inhalation of conidia as evidenced by the sinopulmonary involvement in several patients (63); and (ii) cutaneous, as in cases following cellulitis of the toe or finger, in catheter-related infections, and in patients with burns (72, 106, 243). The prevalence of *Fusarium* spp. in grain foods and the involvement of the gastrointestinal tract in some cases raise the possibility, though unlikely, of a gastrointestinal route of infection (7, 119). Thus far, *Fusarium* spp. are the only opportunistic molds that can be easily recovered from the bloodstream (7, 137). Usually, patients with positive blood cultures tend to have concomitant skin lesions. It has been speculated that the toxins produced by *Fusarium* spp. may enhance the breakdown of tissues and thus facilitate entry of fusaria into the systemic circulation (137). It is also possible that the growth of *Fusarium* spp. may not be inhibited by blood components in cultures as are *Aspergillus* spp. (137). These and other hypotheses are being examined in a rabbit model of systemic fusarial infection in which the organism can be regularly isolated from the bloodstream (7).

Histopathologically, fusarial infections may mimic any number of other mycoses exhibiting moniliaceous, septate, branching or nonbranching hyphae. Because of these morphologic similarities, identification of the fungus obtained from cultures is required to establish a fusarial etiology (6). Immunohistological staining has been successfully used to diagnose tissue invasion (161). Like *Aspergillus* spp., *Fusarium* spp. have a propensity for vascular invasion, resulting in thrombosis and tissue necrosis.

Clinical picture. The disseminated infection by *Fusarium* spp. usually presents as persistent fever unresponsive to broad-spectrum antibiotics in a profoundly neutropenic cancer patient (6). The infection can involve almost any organ. Sinusitis and/or rhinocerebral infection, endophthalmitis, or pyomyositis may be the presenting problem. In the proper setting of immunosuppression, several findings should raise the index of suspicion for *Fusarium* infection. These include a preceding or concomitant toe or finger cellulitis, the presence of cutaneous or subcutaneous lesions, and the growth of a mold from a blood culture. Three types of cutaneous lesions can be observed: multiple erythematous subcutaneous nodules (Fig. 25), which are very suggestive of *Fusarium* infection in this setting; painful erythematous maculas and papules with progressive central infarction (Fig. 26) similar to the ecthyma-gangrenosum-like lesions observed with disseminated aspergillosis; and target lesions consisting of ecthyma-gangrenosum-like lesions surrounded by a thin rim of erythema (Fig. 27). The target lesion is only occasionally observed, but it has not been associated with other opportunistic mycoses and could thus be a useful diagnostic clue. Extensive cellulitis of the face or of the extremities with or without fascitis may also occur.

The high (60%) rate of isolation of *Fusarium* spp. from the bloodstream is in sharp contrast to the rare (<5%) isolation of *Aspergillus* spp. or other opportunistic molds in similar clinical conditions. Similarly, more than two-thirds of patients with disseminated *Fusarium* infection have skin lesions compared with the rare occurrence (<10%) of such lesions in disseminated aspergillosis (6, 137).

Upon recovery from myelosuppression, the infection may either resolve completely or become chronic and localized to sinuses, lungs, eye, brain, joint, or muscle (237), with the potential for relapse and dissemination upon reinstitution of cytotoxic chemotherapy (137). A small subset of patients with hematogenous infection but without organ involvement has been observed (6). These patients have had a successful outcome when antifungal therapy was promptly instituted and the central venous catheter was removed. Whether response was related to the short duration of neutropenia or to the therapeutic measures taken remains to be determined.

Outcome. The status of the host and the extent of the infection are the most important factors predicting the outcome of *Fusarium* infections. Among 58 episodes of disseminated fusarial infection that developed in 53 patients (3, 4, 16, 51, 63, 64, 72, 87, 143, 145, 189, 190, 201, 219, 237), 17 had a successful outcome. The improvement in 16 of these patients was associated with the recovery of the bone marrow function. Only one neutropenic patient appeared to have cleared the infection while still neutropenic following chemotherapy and autologous bone marrow transplant. The infection had developed while the patient had been receiving alternate-day antifungal treatment with amphotericin B and daily rifampin and fluorocytosine. Response was achieved after 6 weeks of amphotericin B, rifampin, granulocyte-macrophage colony-stimulating factor, and granulocyte transfusions while the neutrophil count remained below 0.25×10^9 per liter (16). Hence, successful outcome is related to the control of the underlying disease and recovery from neutropenia. Age, sex, dose, and duration of intravenous amphotericin B, presence or absence of positive blood cultures or skin lesions, and the *Fusarium* spp. involved are all factors that appear to be significantly less related to outcome than host immunity. Surgical resection of infected tissue, when possible, may be an important component of therapy. Limited experimental and clinical experience suggests a therapeutic benefit from the antifungal triazole, SCH39304, which is no longer available (10). Hence, optimal therapy remains to be determined. Given the overall grim prognosis for patients with disseminated infection, effective preventive measures are urgently needed. Infection control policies aimed at reducing the number of airborne fungal conidia in the hospital setting should be properly implemented. Prophylaxis with novel antifungal agents that have good activity against *Fusarium* spp. and shortening the duration of neutropenia with colony-stimulating factors (43) may also prove useful for preventing these devastating infections. *Fusarium* onychomycosis should be treated aggressively, including nail removal in those patients with hematologic malignancies undergoing treatment with cytotoxic chemotherapy with or without bone marrow transplantation. This approach could decrease the risk of developing disseminated *Fusarium* infections during the periods of neutropenia.

Susceptibility of *Fusarium* Species to Antifungal Agents

In vitro, the inhibitory activity by miconazole, itraconazole, and fluorocytosine for *Fusarium* isolates is poor (186). Amphotericin B and natamycin are the most active agents. However, in vitro susceptibility or resistance to these antifungal agents may not predict the clinical outcome of *Fusarium* infection. In our model of murine systemic *Fusarium* infection, amphotericin B at a dose of 1 mg/kg/day was unable to alter an ultimately fatal outcome when the treatment was commenced 1 h after inoculation of a clinical isolate of *F. solani* (5).

CONCLUSION

The two most important taxonomic systems for *Fusarium* species are those of Wollenweber and Reinking and Snyder and Hansen. Other systems that have been used are compared with these two. At present, one must rely on morphological characters for taxonomy, but this should change in the next 5 to 10 years as molecular techniques are applied to the taxonomy of this important genus. Problems such as cultural mutation are discussed along with the difficulties presented by this phenomenon. Several *Fusarium* species are toxigenic, and the mycotoxins and mycotoxicoses produced by these fungi present a potential health problem. Many of the toxins produced by these fungi are not yet characterized chemically. Toxins produced by *F. moniliforme* are discussed separately because a group of mycotoxins produced by this fungus are found readily in corn and are carcinogenic in rats. They pose a potential threat to human health.

Human infections by *Fusarium* species can be superficial or limited to single organs in otherwise healthy patients. Such infections are rare and tend to respond well to therapy. By contrast, disseminated fusarial hyalohyphomycosis has emerged as a significant and usually fatal infection in the immunocompromised host. Successful outcome is determined by the degree of immunosuppression and the extent of the infection. These infections may be clinically suspected on the basis of constellation of clinical and laboratory findings, which should lead to prompt therapy, probably with one of the newer antifungal agents. Perhaps the use of such agents or the use of colony-stimulating factors may improve the outcome of this devastating infection. However, until new approaches for treatment develop, effective preventive measures are urgently needed.

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